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CONTRIBUTIONS

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PATHOLOGICAL LABORATORY

ALDRED SCOTT WARTHIN, PH.D., M. D.,
DIRECTOR

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SYPHILIS OF THE PANCREAS, WITH REFERENCE TO THE COINCIDENCE OF SYPHILITIC PANCREATITIS AND DIABETES

By ALDRED SCOTT WARTHIN, Ph.D., M.D.
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(Preliminary Report)

Syphilis of the pancreas is regarded as a very rare affection by practically all recent writers of text-books on pathology and internal medicine. In the very latest American text-book of pathology, MacCallum states that the pancreas is rarely involved in acquired syphilis; and in the Osler-McCrae *Modern Medicine* Opie, in his paragraph on "Syphilis of the Pancreas," says that the pancreas is rarely the seat of gummata as the result of acquired syphilis and that there are no data with reference to the symptoms or diagnosis of syphilis of the pancreas. He does not even suggest the possibility that syphilis may be an etiological factor in the production of chronic interstitial pancreatitis—and hence possibly concerned in the causation of diabetes. All recent text-books and articles on syphilis make the same statements as to the extreme rarity of syphilitic disease of this organ.

These statements as to the rarity of syphilis of the pancreas are all based upon the old pathological criterion of syphilitic disease—*the gumma*. This is the pathology of forty years ago, and should be abandoned today when modern spirochete studies have shown that the *common pathology of syphilis is not the gumma but is a mild chronic interstitial inflammation leading to parenchymatous atrophy, degeneration and fibrosis*. It is the gumma that is rare; syphilitic inflammation and fibrosis are extremely common lesions, not only in the heart, aorta, and testes, but also in the pancreas. It will probably also be shown that such syphilitic inflammations are not uncommon in the stomach and other organs in which syphilis is now supposed to be of rare occurrence because gumma of these organs is rare. Likewise, in the nervous system the occurrence of gumma is relatively very rare compared to the destruction of nerve cells, proliferations of neuroglia, perivascular infiltrations, and sclerosis of vessels, due to the localization of Spirochæta pallida. My attention was first drawn to the occurrence of syphilitic inflammation of the pancreas by the fact that in 41 cases of latent syphilis studied by me there were 2 cases of diabetes in which the pancreas showed marked interstitial pancreatitis, both inter- and intralobular, with hyaline fibrosis of the islands of Langerhans. Spirochetes were demonstrated in the myocardium of both of these cases, and in 1 they were also found in the pancreas. Active syphilitic lesions were found in the myocardium, aorta, adrenals, and testes of these 2 cases.

Because of this coincidence of pancreatic syphilitic lesions and diabetes 4 other autopsy cases of diabetes occurring in our service since 1907 were studied and were found to show the same concurrence of syphilis. In 2 of these cases spirochetes were also found in active areas in the myocardium; the material from the remaining 2 cases was not examined by the Levaditi method, but active syphilitic inflammations were present in myocardium, aorta, and pancreas (and testes in 1 of these cases, the other being a female).

The diagnosis of syphilis in the 6 cases of diabetes was made upon histological changes alone in 2 cases; and in the other 4 cases upon the presence of precisely similar histological lesions in the heart containing the Spirochæta pallida, as shown by Levaditi's method. In 1 case similar histological lesions in the pancreas showed the presence of spirochetes. These same lesions were found in the pancreas in all 5 remaining cases; but no examination for spirochetes has as yet been carried out. Because of the pancreatic lesions found in these 6 cases of coincident syphilis and diabetes, the pancreas in each of the remaining 39 cases of latent syphilis was then more thoroughly studied, and it was found that this organ was not normal in any one of the old cases of syphilis, but that it presented a more or less severe pancreatitis. The study of the pancreas in latent syphilis, as well as in active clinical cases, has been carried back in our autopsy material to embrace 150 cases of syphilis; and the same result has been obtained—not a single autopsy case of syphilis has shown a normal pancreas. The lesions vary greatly in extent and degree, but are essentially the same. They may be described as follows:

PANCREATIC CHANGES IN LATENT AND ACTIVE SYPHILIS. When the pancreas of each of the 6 cases was given a more detailed study than that made for the autopsy report, it was found that the pathological changes were essentially the same in all, but varying in degree. Briefly, these changes may be classified as follows:

1. Atrophy with fatty infiltration (fatty atrophy), involving particularly the tail and body of the organ.

2. Increase of stroma, both inter- and intralobular, particularly marked about the ducts, and extending along the intralobular ducts between the acini and presenting the picture of a chronic interstitial inflammation, is shown in all 6 cases. This is also most marked in the splenic end and body of the organ. The increase of stroma is not uniform but patchy. Normal lobules are side by side with lobules showing a marked fibrosis; and many sections from different blocks may show no increase of stroma at all. Large areas, particularly in the head, appear normal. The lobules showing the increase of stroma are smaller than normal, and contain adipose tissue cells. Occasionally completely fibroid areas are found in the more severe cases.

3. Inflammatory infiltrations, usually small in size, were found in every case, both in the interlobular connective tissue and within the lobules. The cells are almost wholly mononuclears, small and large lymphocytes, and plasma cells. Polynuclears and eosinophiles are rare. The seat of the infiltration is always in a loose, semifluid, proliferating connective tissue, resembling edematous connective tissue, and containing epithelioid fibroblastic cells. These areas are precisely like those in the myocardium containing colonies of spirochetes. In such active inflammatory areas were the spirochetes found in Case III.

4. Changes in the islands of Langerhans were present in all 6 cases. In all, the islands are undoubtedly greatly diminished in

number; in 2 cases only a few islands remained. Particularly in the tail of the organ is the total or nearly total disappearance of the islands notable. In 2 cases the remaining islands showed a marked hyaline fibrosis. Opie's hyaline degeneration of the cells of the islands was not seen in any case. The islands are destroyed by a connective-tissue proliferation which soon becomes fibroid and hyaline. A number of hypertrophic islands were seen in 1 case. No inflammatory infiltrations were found about the islands. It is clear that the destroyed islands are replaced by irregular masses of fibrous tissue showing no remains of the island structure.

5. The acini in all 6 cases also showed marked changes. In many lobules atrophic acini are present, particularly in those showing marked fibrosis. The majority, however, are larger than normal, this increase in size being very marked in many lobules. The nuclei are larger and the protoplasm shows a marked increase of zymogen granules. Occasionally acini with hyaline protoplasm staining deep red with eosin are found.

6. Numerous structures looking like newly formed islands are found in the areas showing most marked fibrosis and inflammation. At first glance they were interpreted as such. Minute study showed them to be new-formed lobules of acini arising from the ducts. Their origin from the epithelium of the latter can be easily demonstrated. In some cases they have been seen developing inside large dilated ducts. In their earlier stages they very much resemble the islands of Langerhans, because of the small size of their cells, collapsed lumina, and deeply staining nuclei; but centro-acinar cells are found within the undeveloped lumen of the acinus, and they have not the vascular arrangement of the islands. All stages can be traced between these newly formed lobules and large adenoma-like structures with dilated lumina containing centro-acinar cells. They undoubtedly represent regenerative attempts, a new formation of acini from the duct epithelium. In these 6 cases I have found no positive evidence of any new formation of islands. In 1 case (Case VI) very large islands were found and were interpreted as hypertrophic.

7. The bloodvessels show in all cases varying degrees of sclerosis.

8. The ducts are often dilated and show thickened walls. Cystic

ducts are present in every case, and are probably retention cysts of intralobular ducts due to the fibrosis. In one of these papilliferous growths were seen.

The essential pancreatic pathology is the same in all of the 150 cases of latent syphilis, congenital or acquired. There is in all a more or less diffuse or patchy pancreatitis and fibrosis, both interlobular and interacinar. There is a more or less marked atrophy of the organ, usually associated with fatty infiltration of the stroma. With these changes there is marked disappearance of the islands of Langerhans with hyaline fibrosis of the islands. Opie's hyaline degeneration of the islands was not seen in any case. The hyalin of the islands is connective-tissue hyalin—a fibrosis with hyaline change in the connective tissue. Localized lymphocyte and plasma-cell infiltrations occur in all, from very slight collections up to large areas. Fibroblastic proliferation of the stroma occurs within and between the lobules. The rudimentary lymphoid nodes are hyperplastic. Compensatory hypertrophy and regenerative new-formation of acini from the ducts is found in practically all cases. No new-formation of islands was observed, although apparently hypertrophic islands occur in many cases. The newly formed acini in certain stages very closely resemble islands, and such new-formations have no doubt been frequently interpreted as new islands. This is probably true of the illustration shown in Opie's article in *Modern Medicine*. The structures shown there as new-formed islands, are, I feel sure, only newly formed acini. Close study will show the presence of intra-acinar cells and the absence of the vascular relations of the island.

The degree of extent and severity of these changes varies in all cases. In the most severe cases there may be a most marked fibrosis of the gland with but little normal pancreatic tissue remaining. In the majority of cases the process is essentially patchy and scattered. Normal lobules are found side by side with those showing very marked interstitial fibrosis and atrophy. Many sections from different portions of the gland may have to be examined before areas of pancreatitis are found. Such areas are always more numerous in the tail and body of the organ than in the head.

Two important questions at once arise: Are these changes characteristic of syphilis; and what is their relation to diabetes. It is certainly interesting and suggestive, to say the least, that in 150 cases of old latent syphilis there should be 6 cases of diabetes in which the pancreas showed precisely the same pathological changes as are found in this organ in the other cases of syphilis. Is this coincidence purely one of chance?

As to the specificity of the histological changes, I believe that the active areas of lymphocyte and plasma-cell infiltration, with slight fibroblastic proliferations frequently myxomatous in type, with vascular proliferations and obliterations, are in themselves sufficiently characteristic to warrant a diagnosis of latent syphilis from the histological picture above. I know of no other etiological factor for these histological changes. They occur in the bodies of all syphilitics. I have never found them in any other form of infection or intoxication. They are precisely similar to the changes found in the meninges, myocardium, aorta, adrenals, testes, intestinal wall, mesentery, etc., in which spirochetes have been repeatedly demonstrated; and in 1 case we have found spirochetes in these pancreatic lesions. The ultimate fibrosis may be the same as that resulting from arteriosclerosis, due to lead-poisoning, age, etc., but the active areas are, to my knowledge, characteristic of spirochete localization and action. In a number of cases of advanced arteriosclerosis, in which no active lesions of syphilis could be found anywhere in the body after ordinarily careful routine examinations, interstitial fibrosis and sclerosis of the pancreas were also present. It is impossible to say in the absence of active areas that these changes were not of syphilitic origin. The question of the existence of a non-syphilitic arteriosclerotic fibrosis of the pancreas must, therefore, still be an open one.

This fact remains: The pancreas in all cases of latent syphilis is affected in the same way that all other organs and tissues are involved in the general infection. Latent syphilis is a general process; its lesions occur in all organs, more marked in certain organs as the heart wall, aorta, pancreas and testis, in all cases; while in individual cases certain organs (brain, cord, etc.,) are more severely involved. But the heart, aorta, pancreas, adrenals and testes of the paretic and tabetic always show syphilitic lesions and spirochete localizations. Nothing is of greater importance for the clinician to recognize at the present time than the fact that *old syphilis means generalized infection;* and that pathological lesions occur in all organs. *But these lesions are not gummas; they are slight, mild, very chronic interstitial inflammations with corresponding atrophy and parenchymatous degenerations.*

I believe that syphilis is the most common cause of *chronic interstitial pancreatitis*, and that such pancreatic lesions will be found in the pancreas of all cases of old latent syphilis. Only one other pathologist seems to have recognzied this; C. Steinberg (*Aschoff's Pathologische Anatomie*, Band ii) says that syphilis leads frequently to interstitial inflammation and induration of the pancreas. As to the etiological relationship of syphilitic pancreatitis to diabetes mellitus, the problem must still be considered unsettled. Apparently just as marked interacinar pancreatitis and fibrosis, with hyaline changes and disappearance of the islands, occurs in *non-diabetic* syphilitics as in the diabetics. It is, of course, very difficult to estimate comparatively the degree of change in a given pancreas by the examination even of a large number of sections made from different portions of the organ. Complete serial section-studies of the pancreas from diabetic and non-diabetic syphilitic cases might reveal that in the former the degree of change is greater than in the latter. Or perhaps, after all, the pancreatic changes in themselves are not the only factor responsible for the development of the diabetic complex, and that possibly associated changes in liver, adrenals, hypophysis, etc., may be necessary to produce the diabetic phenomena.

In conclusion, the pancreas always shows lesions in old latent syphilis, acquired or congenital. Syphilis is the most common cause of the interstitial interlobular and interacinar pancreatitis with fibrosis and disappearance of the islands of Langerhans so frequently associated with diabetes that some writers have regarded it as part of the essential pathology of this affection. The exact relationship of this pancreatic pathology to diabetes is, however, still an unsettled problem.

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1916, xiv, p. 14.

10 (1188)

Histological study of the testes of guinea pigs showing lead blastophthoria. Preliminary report.

By **Carl Vernon Weller, M.S., M.D.**

[*From the Department of Pathology, University of Michigan.*]

In an earlier report we have shown that the continued administration of small doses of lead produces a definite blastophthoric effect in male guinea pigs; and that the lead blastophthoria thus induced manifests itself in the offspring by a reduction of approximately twenty per cent. in the average birth weight, by an increased number of deaths in the first week of life and by a general retardation in development such that the offspring of lead-poisoned males often remain permanently underweight. The testes of these chronically lead-poisoned guinea pigs have now been examined in sufficient numbers to warrant a preliminary report.

In a majority of the cases examined no histological differences can be detected between the testes of lead-poisoned guinea pigs and those of normal controls. Spermatogenesis appears to take place along normal lines and at a rate which seems not unlike that in normal pigs. This observation is in no degree incompatible with a state of true blastophthoria since it is to be expected that if fertilization takes place at all, the spermatozoa will show no great variation from the normal as far as their appearance is concerned. The reason for the inferiority of the offspring is to be sought rather in qualitative changes in the germ plasm.

In a limited group of instances, in which the male guinea pigs became sterile during the administration of lead, histological examination of the testes shows a complete aspermatogenesis with marked atrophy and vacuolar degeneration of the germinal epithelium. There is an attempt at cell division which results in multinuclear giant cells, evidently comparable to spermatocytes, but division of the protoplasm appears to lag behind that of the nuclei and spermatids and spermatozoa are not produced.

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25 (1203)

The new-formation of hemal nodes in the omentum and mesentery of the dog after splenectomy and ligation of the splenic veins. (Preliminary report.)

By Aldred Scott Warthin, Ph.D., M.D.

[*From the Pathological Laboratories of the University of Michigan, Ann Arbor.*]

The question of the new-formation of splenic or hemolymph-node tissue in the dog after splenectomy has been opened up again by Meyer,[1] who, as the result of the findings of eight dogs examined after splenectomy, at periods of 30, 41, 53, 77, 89, 98, 112 and 126 days after the operation, found no changes in the lymph-nodes, either of the nature of a hyperplasia or regeneration. Doubt was, therefore, cast upon the work of preceding investigators, notably that of Tizzoni.

During the years 1910–13 several series of experimental investigations in regard to this point were carried out in my laboratory, with results as yet unpublished. These are now presented here in the form of a preliminary report.

Results of Splenectomy.—Nine dogs were splenectomized and examined as follows: Three one week after the operation; three two weeks after, and three one month after. In no dog was there the slightest change apparent in the lymph-nodes of any part of the body.

Five dogs were splenectomized and examined eight months after the operation. In one dog the lymph-nodes and hemolymph-nodes were larger than they had appeared to be at the time of operation when these nodes were examined as carefully as they could be. No new-formation of hemolymph-nodes was seen.

Five dogs were splenectomized and examined eight and a half months after the operation. No hyperplasia and no new-formation of lymph-nodes was seen.

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[1] *Journal of Experimental Zoölogy*, 1914.

Five dogs were splenectomized and examined nine and a half months after the operation. In one dog there was distinct enlargement of lymphatic and hemolymph-nodes, but no new-formation.

Results of Ligation of Splenic Veins.—In eight dogs the splenic and gastrosplenic veins were ligated as completely as possible. The animals were examined at periods of one week, two weeks, three weeks, one month, three months, one year, one year and a half, and two years after the operation. These animals were carefully examined at the time of operation for the presence of hemolymph nodes or accessory spleens in the gastrosplenic and great omentum, as well as in the peritoneum and mesentery. No changes in the lymph nodes and no new-formation of hemolymph or splenic tissue was found in the first four dogs. In the dog killed three months after the operation the prevertebral lymph nodes and hemolymph nodes appeared to be slightly enlarged. In the dog examined one year later the prevertebral nodes were much enlarged, but no new formation was noted.

In the dog examined eighteen months after ligation of the veins the prevertebral hemolymph nodes were very hyperplastic, and the gastro-splenic and great omentums were strewn with small reddish points that microscopically present the appearance of developing hemal nodes. In the dog killed two years after the ligation very remarkable changes were found, the omentums, mesentery and peritoneum in the upper left quadrant were strewn with innumerable red nodes, varying in size from that of a pinhead to that of a pea, and in two cases, as large as a cherry. These large ones had all the gross appearances of accessory spleens; but *they had not been present at the time of the operation.* Microscopically these nodes presented all stages of transition in the development of hemal nodes, from the minute dilated lobule of sinusoidal capillaries in the fat tissue up to the fully developed hemal node resembling an accessory spleen. These nodes were precisely the same as those in the preceding case. In both cases the spleen was atrophic.

Conclusion.—Splenectomy in dogs is not comparable in its effects upon the lymph nodes to the same operation in sheep and goats. In only two out of twenty-four dogs was any hyperplasia of the lymph nodes found, and no new-formation of hemolymph-nodes or splenic tissues.

Ligation of the splenic veins seems to produce much more decided results after the lapse of one or two years following the operation. Three out of eight dogs showed marked hyperplasia of the prevertebral nodes, and the two cases examined after longest intervals showed a new-formation of hemal nodes in the splenic region, the largest newly formed nodes resembling accessory spleens. These structures were not present at the time of the operation.

They are not inflammatory in character.

Individual dogs must have different capacities for hyperplasia and regeneration. The minute capillary plexuses from which these nodes arise may represent preformed accessory spleen anlage.

Tizzoni's statements are hereby confirmed and Meyer's objections negatived.

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26 (1204)

A study of the lipin-content of the liver in two cases of pituitary dystrophy. (Preliminary report.)

By **Aldred Scott Warthin, Ph.D., M.D.**

[*From the Pathological Laboratory of the University of Michigan, Ann Arbor.*]

Studies of the lipins in the curious obesity characteristic of hypopituitarism have not as yet been made. In the case of two autopsies upon bodies showing this condition microchemical studies have been carried out by the writer.

One case was a boy of eighteen showing infantilism, obesity and loss of sight (dystrophia adiposo-genitalis). Died after attempted removal of pituitary neoplasm (adamantino-carcinoma); the second case was a man of 29 years, with loss of vision, staggering gait and disturbed mentality. Acromegalic symptoms with secondary hypopituitarism. Round-cell sarcoma of base of skull destroying a hypophysis adenoma.

Both bodies showed very marked post-mortem increase of temperature; the source of the heat-production apparently being localized in the panniculi and fatty livers.

Gross Appearances of the Fat.—Panniculi thick, in large coarse lobules; when first cut it was glistening, translucent, very firm and light buffy yellow in color. As it cooled it became more buff in color, opaque and very hard. The livers of both cases were large, mottled red and yellow, with fatty shine.

Microscopical.—Frozen sections examined optically showed the presence of numerous small anisotropic droplets in liver, adrenals, panniculi, intima of aorta, and elsewhere. In the liver the fine anisotropic droplets are chiefly in the central and midzonal regions. They are present also in a narrow border of preserved liver cells in the peripheral zone. Larger isotropic droplets are scattered irregularly through the lobule, usually occurring in groups. There is in both cases a peculiar necrosis of the inner portion of the peripheral zone (intra-peripheral necrosis).

Staining with *osmic acid* gives a pale gray tint to the fine anisotropic droplets, while the larger fat-drops stain a deep brown-black.

Sudan III stains the fine fat droplets a peculiar brownish red; while the larger fat droplets take a deep brick-red to a yellow or pale buff color.

Scharlach R stains the fine fat-droplets a brownish-red, the larger ones a deep bright red.

Nile-blue sulphate stains the majority of the fine droplets a pink or lavender color. The majority of the larger droplets stain red, some pink, some pink-violet, some purple, some deep blue.

Indophenol. No differential staining shown.

Benda's Method. Gave no differential reaction.

Stains for fatty acids and soaps negative.

Simple staining with hematoxylin and eosin showed a typical ground-glass appearance in the cells containing the fine fat droplets.

From these fat reactions it is evident that the livers of these two cases of dyspituitarism show an unusual lipin content. The presence of numerous anisotropic droplets, staining a lighter gray with osmic acid, brownish or yellowish-red with Sudan III or Scharlach R, and pale pink with Nile-blue sulphate, makes it very probable that these are cholesterol-esters. Other lipoids may be mixed with these or with the glycerin-esters. The lipin combination may be very complex. Our staining methods do not satisfactorily differentiate these. They permit us to say, however, that these fatty changes are not those of ordinary fatty infiltration, but represent a mixed glycerin-ester and cholesterol-ester lipoidosis. It is evident that many of the liver cells contain cholesterol. Whether lecithin is present it is impossible to say.

This cholesterol lipoidosis was not confined to the liver, but occurs to a marked degree in the adrenals, and to a lesser degree in the panniculi and other organs and tissues (aorta, spleen, etc.). In pituitary dystrophia there occurs, therefore, a peculiar abnormal lipin metabolism characterized by cholesterol infiltration or retention (cholesterol steatosis). The condition may then be compared to the cholesterol infiltrations obtained by overfeeding with cholesterol, to the lipoidosis of diabetic lipoidaemia and that of Gaucher's disease.

In addition the liver shows a peculiar intraperipheral zonal necrosis differing from previously described liver-necrosis. With this necrosis there is associated a fibro-blastic proliferation giving the picture of an early intralobular cirrhosis.

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BY

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University of Michigan, Ann Arbor.

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THE MEDICAL LIBRARY OF THE UNIVERSITY OF MICHIGAN.

ALDRED SCOTT WARTHIN, Ph. D., M. D.,
Professor of Pathology and Director of the Pathological Laboratories
in the University of Michigan, Ann Arbor.

An article upon the Medical Library of the University of Michigan written by Dr. George Dock, in 1905, is prefaced with the following paragraph:—"The Medical Library of the University of Michigan is fifty years old; it contains more than 13,000 volumes, and is, therefore, a 'large' medical library. These facts warrant, perhaps even demand, some account of the condition and work of the library."

In the eleven years since Dr. Dock's article, thus prefaced, was written this library has been more than doubled in content of volumes, these now numbering about 30,000; and its importance as a reference medical library of the first rank has, therefore, been correspondingly increased. Leaving out of consideration the six great medical libraries of the country,—the library of the Surgeon-General's Office (190,300), that of the College of Physicians and Surgeons (105,510), that of the New York Academy of Medicine (100,000), the Boston Medical Library (84,000), the library of the Medical Society of the County of Kings (70,000), and the John Crerar library (65,809),—the Medical Library of the College of Medicine and Surgery of the University of Michigan probably is second in rank of medical libraries belonging to teaching institutions of medicine, that of the Lane Library of Leland Stanford University holding the first place (39,500). The medical libraries of Yale (30,000) and of the University of Pennsylvania (28,315) probably closely contest this position of second rank; and it is not absolutely possible at this time to say with accuracy whether this honor belongs to one of these or to Michigan. At any rate our medical library must be counted as one of the three greatest medical-school libraries in the country; and this position of importance becomes especially significant when the following facts are considered:—

First, its relative youth of sixty-one years; secondly, its steady, albeit slow, growth as a part of the teaching equipment of the State University. Without any special endowment, without any gifts of magnitude, this library has seen a continued healthy growth proportionate to the development of the resources of the State of Michigan, and that of the State University as a whole. Like the Medical College itself, it occupies a unique position as a monument to a State in which education and the means of education have always wisely been fostered. That it should outrank the medical libraries of the great endowed and older Eastern Universities may perhaps be partly explained by the propinquity to these schools of five of the great medical libraries mentioned above; but of the medical schools not possessing the advantages of such propinquity Michigan may well stand proudly in the first rank as possessing a medical library that, not simply from the standpoint of size, but from that of value as a reference library, must be considered as one of the most important collections of medical books in this country.

It is primarily a reference library, being made up almost entirely of sets of journals and periodicals, and monographs having vital interest to medical teachers and investigators. It contains relatively but few of the textbooks and medical writings having a more or less ephemeral value; and fewer volumes still of the older medical literature. It is preeminently a library of *modern medicine*. The evolution of modern medicine from its beginnings in the early part of the nineteenth century to the present day is represented almost completely in this collection. The development of modern cellular and chemical pathology, of bacteriology, immunology, pathological physiology and experimental medicine is practically complete in the volumes comprising this library. It is, therefore, made up almost entirely of journals and periodicals dating from or after the first quarter of the nineteenth century; and these have been chosen with care and discrimination as to their working value. The big and important journals showing the results and progress of medical research were first chosen; money has not been unwisely spent, and space has not been unwisely given to local state and medical society journals of inferior value, or to medical periodicals more or less commercialized in character. We have not had shelf room for these. The limited income, the early appropriations being very small indeed, was in reality a blessing; since, combined with the good sense of those having its early development in charge, this income has been so wisely expended. From the very first the wise policy has prevailed of making it a working library of medical research; and all who have taken part in its administration have continued this policy. Since only a few things could be obtained at a time, the best and most necessary things were the ones chosen. Naturally this development as a practical research collection has resulted in a somewhat one-sided library. Preeminently a working library for the medical investigator, it is greatly lacking in its collection of medical classics, and works pertaining to the older evolution of medicine. It is not yet a library for the cultivated scholar in medicine; and its weakest point is in its lack of cultural appeal.

Reviewing very briefly the early history of the library, and borrowing the chief facts from Dr. Dock's article, we find that the first recorded appropriation for medical books amounting to the sum of $66.00 was made in 1854; but that already in 1855 some of the best European medical journals were being taken. In 1860 twenty-four journals, most of them of the best English and foreign periodicals, were being received. But the growth for twenty years was very slow, being checked by the Civil War, so that in 1871 the medical library contained only 1500 volumes; and at the end of thirty years, in 1884, there were but 2626 volumes and 614 pamphlets. Until 1887 small and irregular appropriations had been made for medical books, but after that year the annual appropriation was never less than $1,000 and has slowly increased until it has reached the present sum of $4,000 with an additional $500.00 from students' annual library fees. For a more detailed statement of the early development Dr. Dock's article in the Medical Library and Historical Journal for 1905 may be consulted.

From the very beginning the wise policy had obtained of expending the meager appropriations for the best and most useful periodicals, particularly those devoted to research, rather than yielding to the temptation to purchase text-books. The foundations of a library of the greatest service to teachers and investigators were thus laid; and by 1891 sixty-one medical periodicals were being taken; but the sets, with one exception, the *Archiv für Anatomie and Physiologie*, were incomplete, beginning only with the year of the annual subscription. No serious attempt, for obvious money reasons, had been made to complete the series.

In 1892 Dr. Dock became chairman of the library committee of the medical faculty, and a period of more vigorous development began. The original policy of building up a reference library consisting essentially of the sets of periodicals most useful to the teacher and reseacher was more actively pursued. By 1895, the most important periodicals at that time taken, were completed from their beginnings, and the new ones subscribed for had in many instances been purchased in full sets as to back numbers. The acquisition of important monographs, hospital reports and bulletins, transactions, Festschrifts, etc., was also pushed as far as the still somewhat limited funds would permit. At the time of writing Dr. Dock's article (January 1, 1905) the library had grown to 13,455 bound volumes; and two hundred and twenty-six medical periodicals were being regularly received, eighty-nine of these being complete from the beginning.

In 1908 the writer followed Dr. Dock as Chairman of the Committee on the Medical Library, and during the last eight years there has taken place the most rapid development of any period in its history. The increase in funds granted made it possible to extend subscriptions and complete practically all incomplete files. The increasing cost of binding has necessitated some discrimination as to the journals to be bound. About sixty proprietary and commercial journals previously received were rejected as unworthy the cost of binding and the shelf room. Their places were filled by the new and important journals in special fields of medicine that have come into existence during this time.

Three hundred and seventy journals of the best class were being regularly received until the interruptions resulting from the war. Of these periodicals and continuations there are one hundred and fifty-nine in the German language (Germany, Austria, Switzerland, etc.), one hundred and thirty in English (Great Britain and colonies, United States and colonies), fifty-nine in French, ten in Italian, while the remaining fourteen are distributed through Scandinavian, Dutch, Spanish, etc.

All departments of medicine, including the most highly specialized are represented by the leading journals in English, German, French and Italian. All of the leading Archives, Beiträge, Centralblätter, Folia, Jahresberichte, Jahrbücher, Journals, Revues and Zeitschriften are present in complete series, as are also the best of the weekly and monthly journals. Likewise, the publications of all important medical societies and associations in these three languages are comprised in this collection. No attempt has yet been made to build up sets of the minor provincial journals, or of the transactions of many societies of secondary importance. The collection is still deficient in Spanish and Spanish-American medical literature, as it is also in the medical literature of the Netherlands. It also lacks complete sets of many of the smaller and earlier American medical journals, particularly the Southern ones. The great majority of its wants, however, are fortunately now such as to be of little value to the medical investigator.

It must be emphasized here that the full importance of the Medical Library of the University of Michigan can be realized only when it is considered in its relation to the University General Library of 352,718 volumes (1915) of which it forms an integral part. From the medical collection proper are excluded many journals in chemistry, physics, pharmacy, sanitary engineering, anthropology, botany, biology, psychology, psychiatry, dentistry, sociology, etc., that should be included in any medical library built up as a complete unit separated from such affiliations with other departmental libraries. The Chemical Library, the General Science Library, that of the College of Dentistry, the collection in the Psychopathic Hospital, etc., as well as a library of several thousand volumes in the School of Homeopathy greatly increase, if not double, the accessible library content of medical material. Were these counted as a part of the medical book material, as they practically are, this library would stand in the sixth rank of American medical libraries. It has always been the policy of the library authorities to discourage the purchase of duplicates out of any library appropriations, hence the distribution among these various departments of the journals most suited to their needs. This has been of advantage in building up a much larger general collection than would have resulted otherwise. As these various departmental libraries, with one exception, are all on the campus near the General Library and Medical College, the inconvenience that might result from such a distribution is not felt. Duplicate sets of journals can, however, be purchased out of departmental budgets (current expenses) when these are especially desired. This will become especially necessary in the case of the clinical departments of the University Hospitals located at some distance from the campus libraries. Duplicates of many of the best current periodicals in English are already kept there.

In addition to the periodicals and continuations the library has also a very complete collection of general works of reference, encyclopedias, dictionaries, indices, bibliographies, reports and bulletins of hospitals, reports and transactions of societies, handbooks, systems, and other standard works of reference. The collection of *Festschriften*, *Arbeiten*, *Contributions*, *dissertations*, *monographs*, etc., has also been greatly increased during the last eight years.

Text-books are now being purchased from the fund made available from the students' fees, each medical student paying a two-dollar library fee annually. It seemed but fair to use this fund in purchasing new text-books as they are published, giving the student the opportunity to examine these before purchasing for himself or to use them as he desires. During the last three years the current text-books in English have been purchased on this fund, and the needs of the medical undergraduates have been more satisfactorily met. This policy has also undoubtedly increased the student use of the medical library.

In addition to the general policy of creating first a reference library for the medical teacher and investigator, the writer has during the eight years of his chairmanship on the Medical Library Committee endeavored to extend its field of usefulness by increasing its cultural appeal to the medical student. Its one-sided development as a reference library makes it preeminently a library for the medical researcher rather than a library for the cultivated scholar in medicine. It has failed in one just as important function,—its lack of cultural influence upon the students who make use of it. This defect had been recognized by Dr. Dock during his service on the Medical Library Committee, and to remedy it he laid the foundations of a good working collection of medical history. Of the older medical literature and the ancient classics the library possessed but few examples, most of these having been acquired by chance gift. There never had been any funds to use for the building-up of this side of the library's function; but with the small amount that he could take for this purpose Dr. Dock gradually secured the best of the medical histories, a number of biographies, and other general works in this particular field. Of great importance was the securement, through his influence, of a gift of one thousand dollars from the Hon. Peter White, then a University Regent, to be used towards the development of a collection of the older medical writers. Only one book, a copy of Harvey's "De Motu Cordis," 1628, had been ordered upon this fund, but not paid for, when Dr. Dock left the University.

The use of the Peter White fund has, therefore, been left to the writer; and through it two hundred and seventy-two volumes representing medical landmarks of all periods have been purchased, in the form of original editions, commentaries, monographs, etc., so that from this material alone it is now possible to conduct a very satisfactory seminary course in medical history. As our curriculum does not include the teaching of medical history the writer has carried this out in the form of an elective Journal Club course in the junior year as a part of the staff work in the department of Pathology. These students have had direct access to the medical stacks; they have come into personal contact with the material, and to some of them this excursion into purely cultural fields has been an inspiration, enriching their intellectual lives.

Another valuable gift in the same field is a recent one from Mr. A. M. Todd, of Kalamazoo, including fine copies of the earliest editions of Hippocrates, Galen, and Avicenna and a number of works on alchemy. This gift adds greatly to the value of the medical history section. Other additions have been made in gifts, chiefly of single volumes, and by purchase, a small sum being applied each year to this department. The earlier gifts in this field are mentioned by Dr. Dock in his article. The development of a collection on tuberculosis has also been a feature of the last eight years.

The Medical Library now occupies the entire fourth floor of the north stack and a part of the same floor of the south stack in the General Library building. The Homeopathic Library is on the floor above it; the majority of the books on Hygiene, Bacteriology, etc., are in the Hygienic Library in the Medical Building, and each subdepartment in the Medical School has a small working library connected with its laboratory. Sets of journals are included in some of these departmental libraries; but for many reasons,—difficulty of administration, increased wear and tear, excessive loss, inconvenience to others, danger of fire, etc.,—these small departmental libraries have come to be somewhat of a problem, and should be restricted to duplicates. Bound sets of periodicals of interest to a number of workers should not be kept in them.

In the main library the medical books are in fire-proof stacks, well-lighted and well-ventilated, with plenty of working room in the stacks themselves. There is a small reading-room for medical students only; in this the current periodicals are kept. In the larger Upper Reading Room there is a separate medical card catalogue and such general works of reference as the Index Medicus, Surgeon-General's Catalogue, etc. All of this is now temporary and will be changed within the year. In the new University Library, the construction of which is now progressing, the Medical Library will have greatly increased facilities; a larger reading room, seminary and exhibition room, and faculty working room in bays along the stacks.

There is no medical librarian and no medically-trained attendants. This is at present our greatest weakness, and undoubtedly has hindered greatly the utilization by the medical students of the valuable resources offered by the book collection. This defect will also be remedied when the library is in its new quarters. In the meantime there has been a noticeable increase in the number of students making use of the medical books. Books can be drawn out over night and Sundays. Works especially recommended or referred to by teachers are gathered together at the distributing desk or made immediately accessible to the student in other ways. Thesis and library research work in some departments as a new teaching development also stimulates the students to an increased use and appreciation of the library.

The Medical Library as a part of the State system of education endeavors also to be of practical use to the practitioners of the State. Books can be drawn out for a limited time by any citizen of the State, the cost of transportation to be borne by the reader. It is also possible for non-resident physicians to obtain references and abstracts by the payment of a nominal sum covering the actual time employed in making these. The Medical Library can do for the practitioners of Michigan what the Surgeon-General's Library can do for investigators throughout the country. Should the practitioner come to the library to do his own abstracting he is given full privileges of the library on the presentation of his card. In every possible way we wish to make the medical library of practical value to the physicians of the State.

The Medical Library of the University of Michigan occupies, therefore, a unique position among the medical libraries of the country. Located in a small city in one of the central States, without endowment and without great gifts, with but a moderate annual budget, developing as an essential and logical part of the school system of the State, it has grown into one of the most important medical reference libraries of the country, in response to the ideals of medical teaching and research held by the men responsible for its development. If to this influence there can be added that of a broader cultural stimulus to the minds of the medical students who take advantage of its resources it will become truly a great medical library.

THE PETER WHITE GIFT

TO THE

MEDICAL LIBRARY

ALDRED SCOTT WARTHIN, Ph. D., M. D.

Reprinted from The Michigan Alumnus
November, 1916

THE PETER WHITE GIFT TO THE MEDICAL LIBRARY

ALDRED SCOTT WARTHIN

The Medical Library of the University has grown greatly during the last ten years, and now with approximately thirty thousand volumes, may be numbered with the first half dozen of the country's most important medical book-collections. From its beginning in 1854 it has been developed as a reference library for workers engaged in medical teaching and investigation; and its appropriations, for many years very inadequate, were wisely expended, not for ephemeral text-books, but for the leading journals and periodicals devoted to the results of medical scientific research. This wise policy has been continued throughout the entire period of its growth, and each successive Committee on the Medical Library has kept up this tradition, and has added new journals as they have appeared, and built up the series of those already begun, until now we can boast practically complete sets of all the important medical periodicals having recognized scientific value. The list of current periodicals is about three hundred and seventy, and from this list have been excluded a number of proprietary or commercialized journals usually counted in other medical libraries. Our present appropriations, while much more liberal than in former years, under normal conditions just permit the renewal of our subscriptions and the year's binding. The students' fees alone are used for textbooks, monographs, systems and similar works of temporary value to the medical student.

This development as a practical working research library has resulted, however, in a somewhat one-sided collection, made up almost entirely of journals and periodicals concerned in the making and development of modern medicine, and dating chiefly from or after the first quarter of the nineteenth century. Only a few of these sets of periodicals go back to the eighteenth century. It is a library of *modern medicine,* and a very complete one. The development of modern cellular and chemical pathology, of bacteriology, immunology, and experimental medicine is given almost completely in the volumes comprised in this collection. But of the equally wonderful growth of anatomy and physiology during the sixteenth, seventeenth and eighteenth centuries, of the rich development of surgery and therapeutics even earlier, and of the great classical fountain-heads of medical knowledge it has but little to offer. Upon its shelves are but few of the pig's skin, vellum and parchment volumes to be found in the older medical libraries, between the covers of which is hidden knowledge often regarded as wholly new today. Preeminently a library for the medical investigator it is not a library for the cultivated scholar in medicine; and consequently is not yet fulfilling all of its functions as a complete and well-rounded library of medicine. It fails in its lack of cultural appeal to the students who come to it for knowledge.

It is a great temptation, at this point, to throw some shrapnel in defense of the theory that a knowledge of the evolution of medicine has some cultural value, not only for the student of medicine, although particularly for him, but for other scholars as well, but the limits of this article do not permit this to be done satisfactorily. The history of medicine is so intimately related to the history of human development in general that they would seem inseparable; but it is practically not taught at all in any American university. Our own medical curriculum ignores it. The appreciation of the cultural value of a knowledge of the older writers in medicine is not, however, dead. From time to time the medical library has had added to its collection some rare or valuable volume of historical interest presented by some one to whom the old book had made its appeal. From the libraries of Drs. Ticknor, Dorsch, Ford, Doane, Bates, Jewett, Pilcher, and others, particularly from Mr. A. M. Todd of Kalamazoo, have come the prized volumes making up the nucleus of our collection of the older literature of medicine.

PETER WHITE, A.M. (honorary), '00,
Regent of the University, 1904-1908.

Dr. George Dock was the first of the faculty members taking part in the development of the library to realize fully its one-sided tendency and to remedy it by building up a collection of books devoted to medical history and bibliography. During his connection with the library a very good working collection of medical history was begun. In the development of this cultural feature of the medical library Dr. Dock had the good fortune to excite the personal interest of the Hon. Peter White, at that time a member of the Board of Regents. Mr. White appreciated fully the great need of the library for a collection that would arouse in the medical student a desire for a more intimate acquaintance with the great landmarks of medical history; but he also recognized the inability of the authorities to supply this need at that time. Convinced of the importance of the matter Mr. White himself did what the Board of Regents felt it could not do then, by making available to the Medical Library fund in 1908 the sum of one thousand dollars to be used for the purchase of original editions of classic writers in medicine and

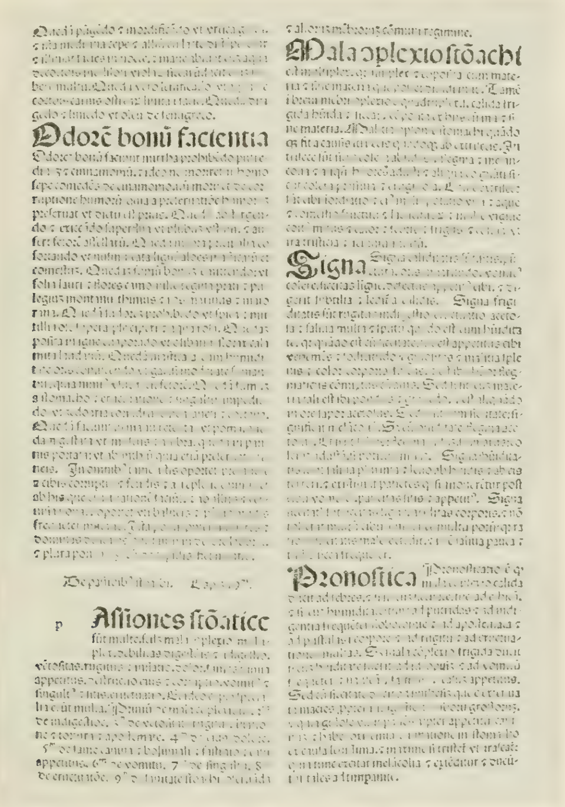
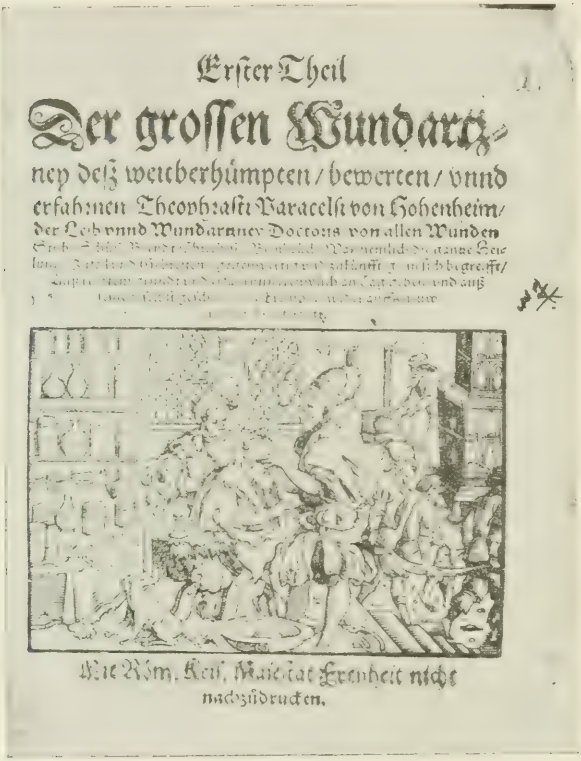


FIGURE I

Specimen page from the first printed edition of the Rosa Anglica of John of Gaddesden, Pavia, 1492, folio in black-letter with contractions, printed in double columns.

of books concerned with the history of medicine. Mr. White died soon after making this gift, and Dr. Dock severed his connection with the University soon after, before any purchases had been made from this fund. Following Dr. Dock as Chairman of the Library Committee, the utilization of Mr. White's gift has been carried out by the writer in accord with the spirit and intent of the gift. Inasmuch as there has existed each year in the Junior medical class a group of usually about a dozen students taking part in a voluntary course (Journal Club) of medical history, it seemed advisable to use this fund in a way to develop a definitely planned course in the evolution of medical science, by spreading the books purchased through all periods of medical history, obtaining, as far as possible the chief landmarks in each period, and making the original writings not only available to the student, but also aiding him in his comprehension of these by the acquisition also of commentaries, translations, monographs, etc., bearing upon the different writers and periods.



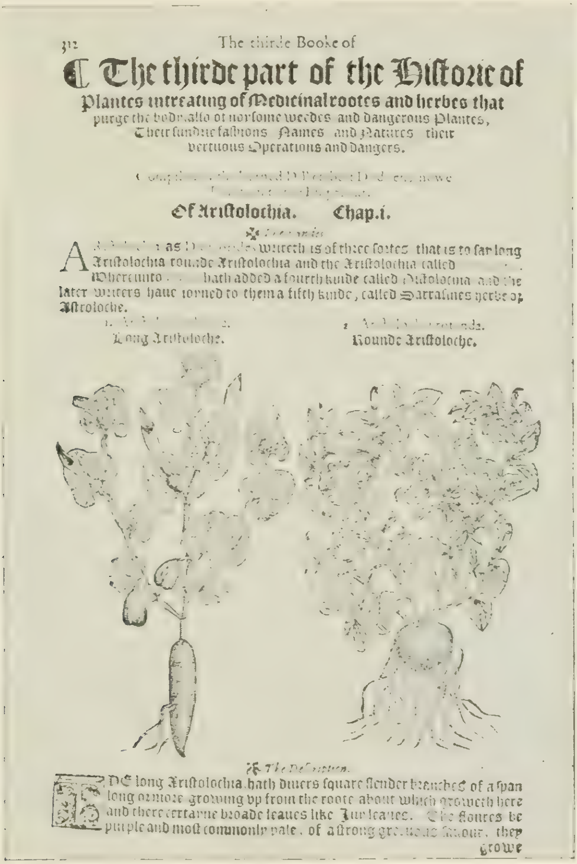
Erſter Theil
Der groſſen Wundartz-
ney deß weitberhümpten / bewerten / vnnd
erfahrnen Theophraſti Paracelſi von Hohenheim /
der Leib vnnd Wundartzney Doctors von allen Wunden

Mit Röm. Keiſ. Maieſtat Freyheit nicht
nachzůdrucken.

FIGURE II

Title-page to the "Erster Theil der grossen Wundartzney" of Paracelsus, Frankfort-am-Main, 1563.

The first purchases made upon this fund had, therefore, to do with early Greek medicine. Sander's "Alkmaeon von Kroton" and Wachtler's "De Alcmaeone Crotoniata" were obtained that the Prehippocratic era might be represented in the notes and commentaries upon the fragments of Theophrastus containing sayings attributed to Alcmaeon, and in the collected references to the latter in Aristotle and other writers. In connection with Kayserling's charming monograph upon "Die Medizin Alcmaeon's von Kroton" these works have been used to show the living inner relationship between ancient Greek medicine and modern medicine; in that, in Alcmaeon there glowed the same divine fire of observation and investigation that is today regarded as the most precious possession of medical science. Alcmaeon is said to have been the first to do autopsies and is probably to be regarded as the father of experimental medicine. Weniger's "Erlebnisse eines Griecharztes," the remaining volumes of the "Corpus Medicorum Graecorum," Daremberg's "Le Médecine entre Homere et Hippocrate," the "Scriptorum Classicorum," "De admirabili operum antiquorum," several texts of Hippocrates, including those of Grimm and Fuchs, fifteen mono-



312 The thirde Booke of

The thirde part of the Hiſtorie of Plantes intreating of Medicinal rootes and herbes that purge the body, allo of noyſome weedes and dangerous Plantes, Their ſundrie faſhions Names and Natures their vertuous Operations and Dangers.

[illegible]

Of Ariſtolochia. Chap.i.

[illegible]

A[illegible] as D[illegible] writeth is of three ſortes that is to ſay long Ariſtolochia rounde Ariſtolochia and the Ariſtolochia called [illegible]. Whereunto [illegible] hath added a fourth kinde called [illegible] and the later writers haue ioyned to them a fifth kinde, called Sarraſines herbe or Aſtrolochie.

1. [illegible] Long Ariſtoloche.
2. [illegible] Rounde Ariſtoloche.

The Deſcription.

The long Ariſtolochia hath diuers ſquare ſlender branches of a ſpan long or more growing vp from the roote about which groweth here and there certayne broade leaues like Iuy leaues. The floures be purple and moſt commonly pale, of a ſtrong [illegible] ſauour, they growe

FIGURE III

Specimen page of Henry Lyte's English edition of Dodoens' famous herbal, published by Gerard Dewes, Pawles Churchyarde, at the Syne of the Swanne, 1578.

graphs and commentaries on Hippocrates, mostly in German, dealing with such subjects as "The Ophthalmology of Hippocrates," etc., that bring home to the modern medical student the ancient knowledge in these varied fields of medicine, offer now a fairly adequate material for seminar work in this period.

The post-Hippocratic and Latin period is represented by the eleven volumes of "Artis medicae principes, post Hippocratem et Galenum" including Hippocrates, Aretaeus, Alexander, Aurelianus, Celsus and Rhazeus, a new edition of Celsus, one of Dioscorides, the chief representative of the Roman Materia Medica (also Mathiolus' Commentaries upon Dioscorides), and other editions of Galen, with fifteen monographs upon his works. Of the post-Galenic period examples of Oribasius, Alexander von Tralles and Paulus von Aegina (Basel edition of 1532) are representative.

Such monographs as Ebstein's "Medizin in alten Testament," "Im neuen Testament and Talmud," Opitz's "Medizin in Koran," Harnach's "Medizinisches in der Kirchengeschicte," Payne's "English Medicine in Anglo-Saxon Times," etc., have also been of the greatest value in Journal Club work.

The medicine of the Middle Ages is represented by examples of Rhazes and Avicenna; the monastic medicine by texts and commentaries of the celebrated Schola Salernitana (11th and 12th centuries), now to be classed among the mere curiosities of medicine. No examples of 14th and 15th century manuscripts or of editions or commentaries could be obtained, with the exception of a copy of the famous "Rosa Anglica" of John of Gaddesden (1280-1361) which was written about 1314, in the seventh year of his lectures which began in 1307. Our copy is an example of the earliest printed edition (Pavia, 1492). It is a folio in black letter with contractions, printed in double columns. It has many marginal notes in Latin, one set in an older form and handwriting. It is in very fair condition, the majority of the pages showing little or no discoloration. An illustration is given of one of these. Gaddesden, it will be remembered, is of particular interest to the general scholar as one of the medical authorities of whom Chaucer's physician had good knowledge:

> "Wel knew he the olde Esculapius,
> And Deiscoride, and eek Rufus,
> Old Ypocras, Haly and Galien,
> Serapion, Razis and Avicen;
> Averrois, Damascien and Constantyn,
> Bernard, and *Gatesden,* and Gilbertyn."

Of these medical classics mentioned by Chaucer, Mr. White's generosity has enabled us to obtain texts of nearly half. But it is not the mention by Chaucer alone that makes Gaddesden's Rosa Anglica a possession of value. While Gaddesden's medicine is largely a compilation from the Greek, Arabian and Jewish physicians it contains many personal observations tending to show that he must have been a practitioner of large experience. His clinical descriptions, as that of ascites, for example, are of high rank; and in his treatment of dropsy by reducing the amount of salt taken in the food he anticipated a very vigorously advocated therapeutic principle of the present day. He is also celebrated for his red light treatment of small-pox. Our copy, unbound, cost one hundred and twenty dollars.

One of the most puzzling and interesting characters of the sixteenth century is Paracelsus. The strange mixture of mystic, fanatic, fighter, charlatan, boaster, and researcher, revealed in his works will make him for all time the subject of questioning as to the amount of esteem actually due him. His great service to medicine was the application of chemical ideas to therapeutics, and the revolutionary stimulus of his conceptions of general theory. Three of his most celebrated works bound together in fine pressed pigskin with old metal clasps were purchased: "Erster, Der Ander und Der

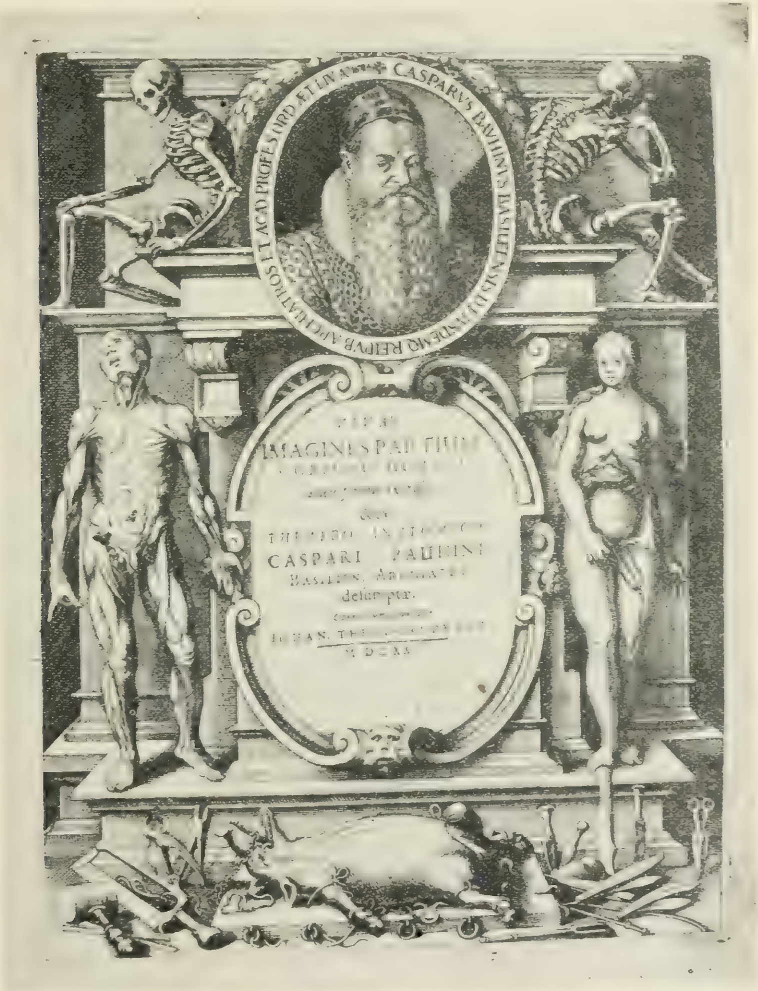
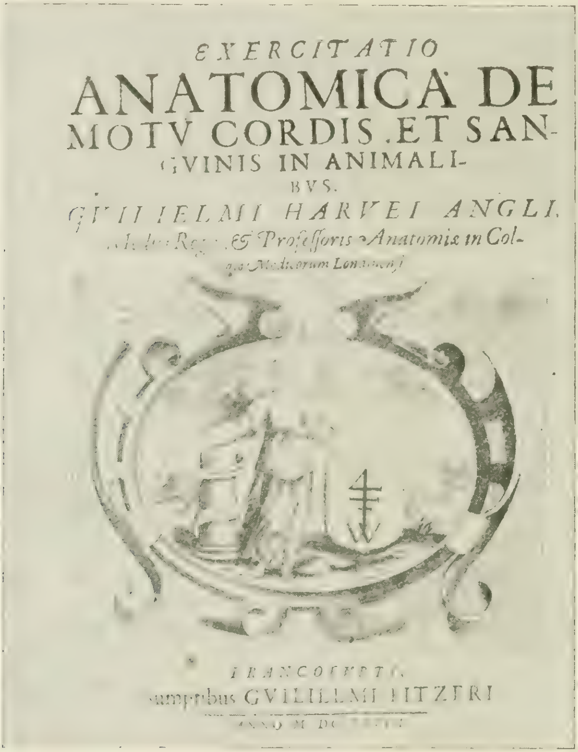


FIGURE IV
Title-page of Bauhin's "Vivae Imagines Partium Corporis Humanis," 1620

Dritte Theil der grossen Wundartzney des weitberhuempten, bewerten und erfahrnen, Theophrasti Paracelsi von Hohenheim," printed in 1563 in Frankfurt-am-Main, by Weygand Han and Georg Raben. The title page woodcut and two in the text are most interesting. Bound with this are the "Spittal Buch," printed by Peter Schmidt of Mühlhausen in 1562, and the "Bader Buechlin," from the same press and in the same year. These are very rare examples of early Mühlhausen printing, and the tracts on bathing contain naive woodcuts of bathers. The illustration reproduces the title-page of the first part of the Wundartzney. For the three in one volume one hundred and ten dollars were paid. Another edition of Paracelsus, "Opera omnia" was also purchased on this fund.



EXERCITATIO
ANATOMICA DE
MOTV CORDIS .ET SAN-
GVINIS IN ANIMALI-
BVS.
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomiæ in Col-
legio Medicorum Londinensi
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI
ANNO M. DC. XXVIII.

FIGURE V

Title-page of William Harvey's "Exercitatio anatomica de motu cordis," "Franckfort-on-the-Maine," 1628.

Herbals are represented in the Peter White collection by an English edition of Dodoens' great work, translated, however, from a French edition, by Henry Lyte, and printed by Gerard Dewes, Pawles Churchyarde, at the Syne of the Swanne, 1578. It is sometimes called the second English herbal. This copy was purchased from the library left by Dr. Samuel Jones of Ann Arbor. A page illustration is given to show the interesting engravings of flowers, of which the book is full.

In another illustration is given the title page of Bauhin's "Vivae Imagines Partium Corporis Humanis," printed in 1620. It is a very characteristic work of the period with its naive anatomical models more or less mournfully contemplating the mysteries of their interiors as revealed by dissection. This was the period of the great anatomical discoveries, and the names of the great writers on anatomy of this time are known to every Freshman medical student because of their association with certain anatomical parts, but in the average case he memorizes and uses such terms as Sylvius, Vesalius, Eustachi, Faloppia, Varoli, Bauhin, and others attached to certain structures without the slightest knowledge of the men whose names still cling to the parts discovered by them. One copy of Bauhin is a very fine one, in a nice old binding and contains numerous interesting copper plate drawings of dissections.

Another rare treasure which was directed our way by Dr. Angell, and purchased through this fund, is a copy of William Harvey's epoch-making work "Exercitatio anatomica de motu cordis," published at "Franckfort-on-the-Maine," 1628, in which Harvey's exposition of the circulation of the blood is set forth, a discovery arrived at after a number of years of observation and experimentation culminating at last in a triumphant act of inductive reasoning. Our copy of this great work is perfect as to text; it was unbound, very brown, and the paper, from washing perhaps, is so delicate that binding or backing the paper with transparent cloth is now impossible. Two hundred dollars was paid for our copy of this remarkable work. The title-page is shown in one of the illustrations accompanying this article.

Altogether there have been purchased through the Peter White fund during these eight years two hundred and seventy-two volumes. It would be a pleasure to speak of each one individually. Each book was bought to fill out some gap in the scheme of a collection primarily designed for the study of the history of medicine. Bindings and press were not made the first consideration, but whenever these could be combined in the work desired they were also considered as educational factors. Only a passing mention can be made of the reproductions of the Leonardo da Vinci anatomical manuscripts, of the copies of Priscianus (1532), Matthiolus (1569), Agrippa ab Netteshym (1600), Alpinus (1601), Licetus (1612), Tulpius (1672), Morton (1696), Sennert the father of Semiotics, a collection of seven herbals, works on the history of tuberculosis, and other valuable books.

To Mr. White's generous and intelligent gift the medical library is indebted for this valuable collection of classic works in medicine that it could not have obtained out of its own appropriations. They have been used with great profit to the small groups of students who have been able to come into touch with them; and in some of these have been the means of creating a more scholarly interest in their chosen profession. Their lives are enriched thereby. And this is the fine thing attached to gifts of this kind that their influence may go on through the years in ever-widening circles, creating here and there some conception of life above the purely utilitarian, stimulating the imaginative and spiritual development, and helping to create the one greatest thing in this life—the cultivated mind.

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THE ROLE OF SYPHILIS IN INTERNAL MEDICINE.*

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Mr. Chairman, Ladies and Gentlemen, Members of the Illinois State Medical Society: I am very appreciative of the honor of being asked to give the Oration in Medicine, and still more appreciative of the fact that a number of members of this association have asked me to speak of the results of my own work on syphilis. Therefore, I have chosen for this afternoon's address the subject, "The Newer Pathology of Syphilis and Its Significance in Internal Medicine." I think I may be safe in saying that the greater part of this audience—certainly the older portion of it—has been contemporary with that wonderful advance in bacteriology and immunology that has characterized the last thirty years in medicine. As we look back over these years, however, we cannot avoid the consciousness of a marked change—or, rather, changes—in our conceptions of infection and the infectious diseases. At first the problem of infection seemed so simple; everything was solved by the discovery of the infective agent. To those of us who entered medicine during the eighties or early nineties there must come memories of the thrills of enthusiasm with which the discovery of each new infective agent was welcomed, and of the optimism thereby engendered as to the ultimate eradication of such agents of infection.

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*Oration in Medicine at the Annual Meeting of the Illinois State Medical Society, at Bloomington, May 9, 1917.

With the discovery of the tubercle-bacillus and the early studies proving the etiological entity of animal and human tuberculosis, of acute miliary tuberculosis, caseous pneumonia, pulmonary consumption, chronic fibroid phthisis and tubercles of the serous membranes; and that many affections of various organs, kidneys, bones, joints, genital organs, etc., were one and the same disease, it seemed to us, in our first confident enthusiasm that the problem of infection had been solved. We hoped and we believed that in a short time the etiological problems of the other infectious diseases would be similarly solved, and that following the discovery of the infective agents it could be but a short time relatively before the human race could be freed from these afflictions.

The literature of the period reflects this optimism as to the victory of scientific medicine over the infectious diseases. Tuberculosis would be conquered in ten years, in one generation, or, perhaps, in two! With the discovery of the typhoid and the diphtheria bacillus, and the other pathogenic organisms that followed in rapid succession, the same attitude prevailed. The problem of infection was simply the infective agent and the damage caused by that agent. If we discovered the cause of infection, we had caught the hare; it was ours, we could cook it.

As our knowledge of bacteriology progressed we found that infection was, after all, not quite so simple a problem—it was not simply a question of the entrance into the body of a harmful agent, and the damage done there by that agent. We came to believe that infectious disease meant more than this—it was also a reaction on the part of the human body.

Studies showing the constant presence of pathogenic organisms in the human body, without apparent damage resulting to the body, or apparent reaction to these organisms—pyogenic cocci in the mouth and other body passages, pathogenic organisms in the gastro-intestinal tract, etc.—led the way toward the recognition of the pneumo-coccus, diphtheria, and typhoid-carrier. The great problem of the germ-carrier was gradually placed before us; and we came to realize that infection was something more than the action of an injurious agent and the response of the body to the damage produced by that agent. From the simpler conceptions of *bacteriology* we advanced to the more difficult problems of *immunology.* Infection gradually came to be regarded as a great complex biological reaction between two living biological systems—the infective agent on one hand, and the human organism on the other. Today we look upon the problem of infection in a very different way from that of twenty-five years ago, and with a conception quite undreamed of at that time. Deeper problems of infection now assert themselves in a most striking way. Today we know that infection means, in many cases, the persistence of the infective organism within the body after all symptoms of the disturbance caused by the former or the reaction of the latter to this damage have disappeared. An apparent "healing" or "cure" of an infectious disease may mean that the infective injurious agent and the human body have entered into a sort of partnership—a mutual compromise, rather than an armed neutrality—in which the body has adapted itself to the infective organism, and the latter has adapted itself to the body. The infective agent remains in the body, for months, for years, or for the remainder of the individual's existence. The infective agent has acquired a saprophytic symbiotic existence; the body has acquired what we call immunity.

Our first important practical knowledge of the significance of such apparently cured infections came in the case of gonorrhea, a disease which in the early nineties was generally thought to be a very mild affection in the great majority of cases. I myself was taught by my clinical teachers of that time that gonorrhea was a simple thing, practically a joke, easily cured. But before the nineties were over this conception of gonorrhea and gonococcus infections had changed. The significance of the gonococcus carrier in the etiology of pelvic inflammations of women—the persistence of gonococci in the genital tract of men, and the later infection of wives—has so changed our conceptions of this disease that today one may hear physicians say they would rather have syphilis than gonorrhea, believing the former infection to be more easily curable than the latter.

But what is true of gonorrhea is true of other infections. Today we realize that the man who contracts malaria is probably a carrier of the organism of malaria for the remainder of his life. The patient who develops a clinically recognizable tuberculosis probably also carries tubercle-bacilli in his body as long as he lives. From the time of our first respiratory infection we carry streptococci in our mouths; a certain number of individuals will continue to carry the pneumococcus, a still smaller number the diphtheria bacillus. The human body is a home for many organisms, not only as far as its passages and cavities are concerned, but also probably in its solid tissues and organs. From lymph-nodes and spleen especially organisms may be obtained, probably constantly; as the diphtheroids and others, regarded from time to time as etiological agents in Hodgkin's disease, pernicious anemia, etc.

What is true of these infections is, I believe, especially true of syphilis. The organism of this disease, the *Spirochaeta pallida,* was discovered in 1903, fourteen years ago. With the discovery of this etiological agent it has been possible to rewrite the pathology of syphilis. The studies of this parasite in human tissues have revealed the fact that in individuals who are apparently well, who have no clinical signs of syphilis, no history of infection, no reactions indicating the presence of active syphilis—negative Wassermann—certain organs and tissues may show the presence of spirochetes corresponding morphologically in every way to the *Spirochaeta pallida;* and associated with these organisms there are slight pathological lesions that do not appear above the clinical horizon. The same thing is true of the organs and tissues of apparently cured cases of syphilis with definite clinical history of infection. Further, in individuals with or without a clinical history of syphilis, who present various pathological conditions, such as myocardial insufficiency, aortic sclerosis, chronic nephritis, diabetes, hepatitis, adrenal insufficiency, and many other vague and obscure conditions not diagnosed at all, the same organism and the same tissue-lesions are present, showing that these conditions are in reality due to syphilitic infection. In all of these spirochete carriers the spirochetes are not absolutely inactive, but are causing some damage. This damage is shown, however, in an entirely different way from that ordinarily accepted as syphilis clinically. These cases are not the ones seen by the dermatologist or syphilologist. They fall within the province of internal medicine when the damage done becomes clinically manifest. The pathology of these lesions is also quite different from that ordinarily accepted as syphilitic. As the result of the discovery of the *Spirochaeta pallida,* and of our ability to demonstrate this organism in the tissues by means of Levaditi's silver-impregnation method, we must greatly alter our old conceptions of syphilis, accept for this infection a new pathology, and include within the range of its clinical manifestations a large number of conditions belonging to internal medicine, the syphilitic nature of which has not before been positively demonstrated.

My studies of syphilis were begun in 1905 with the study of congenital cardiac syphilis, and for a number of years I had an opportunity of collecting and studying a large number of hearts from cases of congenital syphilis; and as the result of that study it was shown that spirochetes could be present in enormous numbers in the myocardium in congenital syphilis without the production of any recognizable histological lesions at all. In other cases there were found associated with the presence of spirochetes various pathological conditions that never before had been recognized as syphilitic in nature.

It was a very natural thing to follow the studies of congenital cardiac syphilis with an investigation as to the occurrence and nature of adult syphilis of the heart. My pathological material from the University Hospital in Ann Arbor was particularly suitable for this study. Although the autopsy service is a relatively small one (30-50 autopsies yearly; recently increasing about three times this number) it was made up largely of chronic cases entering the medical clinic with clinical conditions not in any way suspected of being syphilitic. The pathological study of these autopsy cases has shown that about one-third of them have been cases of active latent syphilis, showing spirochetes associated with pathological lesions not before recognized as syphilitic.

The old pathology of syphilis was essentially the gumma. Before the days of the *Spirochaeta pallida,* when a gumma was found the pathologist could give a positive diagnosis of syphilis; but in the absence of the gumma he could not make such a positive statement. The occurrence of inflammation or fibrosis unassociated by gummatous granulomas could not be taken as certain evidence of syphilitic infection, no matter how strongly their syphilitic nature might be suspected.

Today, I think, we are in a position to make more positive statements. We find the spirochete associated with inflammatory processes showing no gummatous character. We know, therefore, beyond doubt that these lesions are also syphilitic, as much a part of the pathology of syphilis as is the gumma; or rather much more so, because they are much more frequent than the gumma. The newer pathology of syphilis is not the gumma. The gumma is relatively a rare lesion of syphilis. The most common pathological lesion produced by the spirochete is a mild, chronic inflammation, usually minute in extent, but widely scattered, lasting many years, producing a slowly progressive fibrosis and parenchymatous atrophy and degeneration, most commonly found in such important organs as the heart, aorta, adrenals, pancreas, testes, blood vessels and the central nervous system. In the last-named a gliosis rather than a fibrosis of course takes place.

The syphilitic nature of such minute chronic inflammations and fibroses was suspected by the older pathologists. It was the pathologist who first asserted a syphilitic etiology for aortic aneurism, although he could not positively prove this; the pathologist also, before the clinician, was quite sure that paresis and locomotor ataxia were syphilitic. The *orchitis fibrosa chronica syphilitica* of the older writers was also regarded as syphilitic in etiology long before the days of the spirochete. Thickenings of the meninges, sclerotic changes in blood vessels, fibrosis of the heart, and even a general fibrosis of the body have been regarded as syphilitic in origin by some of the great gross pathologists. The assertion of Kolisko, twenty-five years ago, that "the tissues of the old syphilitic are tougher than those of the ordinary man," has received definite proof in these studies. It was one of those astute generalizations based upon many observations of the dead body of which the Rokitansky school of gross pathological anatomists made so many but could not absolutely prove.

My work today has proved the truth of these old suspicions and generalizations. The individual who has become infected with the spirochete of syphilis has throughout his body many foci of spirochete colonization, producing slight local damage and slight inflammatory reactions, leading ultimately to a fibrosis and induration of the connective tissues with more or less atrophy and degeneration of the parenchyma. The resulting functional disturbance may be so slight as never to rise above the clinical horizon. The infected individual may never show any symptoms; indeed, he may never know that he has syphilis. I have no doubt that many syphilitics are wholly unaware of their infection. Just as soon, however, as the functional capacity of the affected organ becomes lowered to a point below that necessary for the general health of the organism clinical manifestations will appear. These will vary greatly according to the location and degree of the syphilitic lesions. In one case it may be the myocardium, in another the aorta, in another the pancreas, and so on. The symptoms may be those of a functional inadequacy of any one of the internal organs. In the absence of a history of syphilitic infection, or in the light of a supposedly old cured syphilis the syphilitic nature of these functional insufficiencies is not recognized.

Our conception of syphilis in the past has been almost wholly dermatological. It is still so today. Enter the case of syphilis, with primary sore on skin and mucous membrane lesions! He is treated as a dermatologic or syphilogic case until his primary sore and his skin and mucous membrane lesions have disappeared; and in the great majority of cases they will usually promptly disappear, whether under the old mercurial treatment, or the modern salvarsan method. In a number of cases they will disappear just as promptly without any treatment. In the majority of cases when these lesions disappear the patient usually regards himself as cured, cannot be induced to continue treatment. for a longer period, and finally disappears from the observation of the dermatologist or syphilologist. Years after he again becomes a patient, most frequently of the internist, but also frequently of the neurologist or psychiatrist. To these he comes with cardio-vascular renal disease, angina pectoris, aortic aneurism, diabetes, nephritis, impotency, vague gastro-intestinal symptoms, headache, early paresis or tabes, pernicious anemia, and many other conditions for which a syphilitic etiology is not suspected, and the true nature of the condition not recognized.

Such was the clinical material in the first group of autopsies studied by me. Forty-one cases out of 148 autopsies showed on microscopic examination the characteristic lesions of syphilitic inflammation, and in the majority of these cases the spirochetes of syphilis were demonstrated in these lesions. In only five of these cases was there a clinically active syphilis; in eleven there was a history of old "cured" syphilis; in twenty-five cases there was no clinical suspicion of the existence of syphilis. The clinical diagnoses in these twenty-five cases were:

Enlarged prostate	3	Diabetes	2
Cancer of stomach	3	Carcinoma of uterus	1
Tumor of intestine	1	Tuberculosis	1
Cystadenoma of ovary	1	Arsenical poisoning	1
Chloroma	1	Arthritis deformans	1
Dementia	1	Pernicious anemia	1
Myocardial insufficiency	2	Peritonitis	1
Chronic valvular lesion	2	Undiagnosed	1
Alcoholic cirrhosis	2		

In all of these forty-one cases the same essential pathology was found. In all the heart, aorta and pancreas showed active minute inflammatory foci, with healing, leading to fibrosis, and with parenchymatous atrophy and degeneration. In all the male cases the testes showed similar lesions. Likewise the adrenals showed almost constantly similar lesions. These organs alone have been thoroughly studied. I have not yet been able to make any study of syphilitic changes in lung, spleen, kidney, gastro-intestinal tract or nervous system; but in the routine examination of sections from these organs similar syphilitic lesions have been found in some of the cases. We have also found similar lesions in the meninges, periosteum, in the mesentery and retroperitoneal tissues. From this original group of forty-one cases the study has been extended to over a hundred and fifty cases of latent syphilis, as far as the heart, aorta, pancreas, adrenals and testes are concerned.

In all of these cases the pathological lesions of old active and latent, recognized or unrecognized syphilis are the same, as will be seen from the microphotographs shown upon the screen. To sum these up briefly, the common pathological lesion produced by the *Spirochaeta pallida* is a minute localized interstitial infiltration of lymphocytes and plasma-cells, in a semi-fluid or myxomatous intercellular substance, with a fibroblastic proliferation leading to fibrosis. As the lesions heal, the connective-tissue becomes hyaline. The inflammatory infiltrations vary from very small groups or cords of cells to larger areas visible to the naked eye. Only rarely do they take on the characteristics of gummata. The gumma is a rare occurrence in the pathology of syphilis. Yet almost all of the statements in our current text-books of internal medicine as to the frequency of syphilis of the viscera are based wholly upon observations as to the frequency of gumma of these organs. Syphilis of the myocardium is rare because gumma of the heart is rare; syphilis of the pancreas is rare, because gumma of the pancreas is rare, and so on. The contrary is proved by the demonstration that these minute infiltrations and resulting fibrosis are due to localizations of the spirochete. These lesions constitute the essential pathology of syphilitic infection. As long as the affected area is still more cellular and less fibrous than normal connective tissue, spirochetes may be demonstrated in the lesion; but as it heals and becomes hyaline, they disappear. The number of spirochetes may be very great in the younger, more active lesions; in the older ones they are usually found in small numbers. The final result of these small syphilitic infiltrations and proliferations in the myocardium is the fibroid heart with its attendant clinical manifestations of angina, myocardial insufficiency, etc. The part of the heart wall most frequently involved is the left ventricular wall anteriorly, just above the apex, the adjacent portion of the septum, and the posterior wall of the left ventricle.

Similar lymphocyte and plasma-cell infiltrations occur in the wall of the aorta, in the adventitia and muscle coat, along the walls of the vasa vasorum. The small arteries of the aortic wall show obliteration; the most marked areas of infiltration are about the veins. In adult syphilis I have never found spirochetes localized in the intima of the aorta. The final result of these changes is the gradual degeneration and fibrosis of the intima, proceeding outwards; an arteriosclerosis that cannot histologically be differentiated from aortic sclerosis due to any other cause. The active lesions should always be sought in the middle and outer coats of the vessel.

Precisely similar lesions occur in the wall of the pulmonary artery. Aneurism of the vessel and its branches may result from syphilitic disease as in the case of the aorta.

In the pancreas of the individual who has latent syphilis, careful search will always show the presence of small areas of interstitial inflammation, characterized by lymphocytic and plasma-cell infiltrations, fibroblastic proliferations, and eventually fibrosis. These inflammations may be diffuse, or scattered; small and insignificant, or more extensive. In diabetic and non-diabetic cases they may be equally very marked. Diminution in number of the islands of Langerhans apparently occurs in all cases of syphilis, and frequently the fibrosis of these islands is very marked, as in some of the diabetic cases. Progressive atrophy of the acini, fatty infiltration, sclerosis of the vessels, and regenerative new-formation of acini from the epithelium of the tubules characterize the pancreatic changes.

In the adrenals small infiltrations of plasma-cells and lymphocytes, thickening of the capsule, sclerosis of the vessels, and excessive lipoidosis of the cortex are found to some extent in all of the syphilitic cases examined. Likewise the testes of all syphilitics examined show a more or less marked intertubular infiltration of plasma cells and lymphocytes, proliferation of the stroma, hyaline change in the basement membrane of the tubules, with atrophy of the germinal epithelium and aspermatogenesis. These changes may be slight and focal; or they may be extensive and diffuse involving the entire organ. The latter may preserve its normal shape, size and consistence.

In the liver about the portal vessels, in the root of the mesentery, in the prevertebral tissues, and elsewhere in the body of the syphilitic there may be found about the blood vessels similar small collections of lymphocytes and plasma cells with slight fibroblastic proliferation, and a progressive fibrosis and sclerosis.

The general pathology of the unsuspected case of syphilis is precisely that found in the recognized case. The pareic and tabetic show precisely the same general pathology. It is very probable that the thorough examination microscopically of the central nervous system will show in all cases of syphilis similar lesions in brain and cord. In a few cases in which I have made routine examinations of these tissues small perivascular infiltrations of lymphocytes and plasma cells have been met with in the brain and cord; that is, non-tabetic and non-paretic cases of syphilis may show small and scattered pathological changes identical with those found to a more marked extent in tabes and paresis. In the latter the changes are so marked that functional insufficiency arises and the clinical symptoms of paresis and tabes rise to the surface; in the former the functional inadequacy does not become manifest.

Such is the general pathology of the spirochete carrier. In all of the cases examined the mildness of the infection, and the tendency of the slight lesions to ultimate healing is very striking. The spirochetes are not very injurious in their action upon the tissues. It is a symbiosis—a partnership in which the human organism obtains immunity—relative immunity—at a certain price, and sooner or later must pay the price in the premature failure or loss of function resulting from the progressive slight injuries extending over periods of years. The important thing is that absolute healing—absolute disappearance of the organisms and complete healing of the inflammatory foci—does not seem to be reached. The syphilitic remains a spirochete carrier to the end of his days, as far as our present knowledge goes. This persistence of the organism may be in part the result of the failure of our therapeutic methods; it may be also the result of the biologic relationship established between the spirochete and the human body through long ages of mutual antagonism and defense.

In conclusion, the importance of this for internal medicine is evident. The internist must recognize syphilis as a possible etiological agent in many internal affections—cardiovascular—renal conditions, myocardial insufficiency, arteriosclerosis, diabetes, adrenal insufficiency, gastro-intestinal affections, etc.—for which today a syphilitic etiology is not generally suspected. The general practitioner has not recognized the clinical importance of syphilis—latent, apparently cured syphilis. Such cases coming to him are not diagnosed as syphilis; the death certificates give "heart disease," etc., as the cause of death. They should be recognized and given their proper name. The older clinicians of twenty-five and thirty years emphasized the importance of latent syphilis in internal medicine in a way that has apparently been forgotten in recent years.

Of the syphilis about us, latent and unrecognized, the greater part is probably congenital and non-venereal in origin. Medicine has yet to learn that syphilis is a family disease. One case of venereal syphilis may produce ten to twenty non-venereal cases. If the disasters of innocently acquired syphilis in the medical profession alone were fully revealed the shock would be great. Today we are still reaping the venereal harvest of the Civil and Spanish-American wars; and the next generation will be reaping a still greater harvest of disease and death if this country actually enters the conflict abroad, if we do not take most vigorous action toward prevention. Such preventive methods must include the emphasis of continence as the only safe method. In the British and Canadian armies the failure to meet this situation from any other standpoint than that of personal prophylaxis has been a disastrous failure. Prophylactic medical methods alone have led to the most frightful incidence of venereal diseases in these forces. I was personally told last winter by a military officer of high rank in the Canadian forces that of the Canadian soldiers returning up to a certain period, ninety per cent came back with syphilis. A medical officer recently returned from England told me of one division of troops of twelve hundred men in a camp in England. At the end of six months, before ever reaching the trenches eight hundred and forty-two of the twelve hundred were said to have contracted syphilis; and yet this medical officer said "We did everything possible for them in the way of personal prophylaxis." Think of the cases of innocent syphilis that will follow this war when the syphilitic soldier returns to civil life and passes the disease on to others, his wife and children! For generations we shall be paying the cost of this infection alone!

As we enter this war we should do so with a higher and more effective ideal of prevention than that of medical prophylaxis. The young men who go into the struggle should be given a better chance—they should be thoroughly instructed in the meaning of venereal disease and in the physiology of continence. I am glad to see that the Council of National Defense has already taken constructive steps in this direction and that Secretary Baker has appointed a special commission that will attempt to attack this great menace from other standpoints than that of medical prophylaxis.

Just here lies the medical man's greatest responsibility. The medical officer who will advocate a higher morality, who will show the possibilities of a biologically clean life is going to render a greater service to his country than the medical man who will tell the young men in his company that "it can be made safe."

Visceral Lesions In Latent Syphilis

(Lantern Slide Demonstration)

By Aldred S. Warthin, M. D.

Ann Arbor, Michigan

Reprint from Mississippi Valley Medical Journal, April, 1917

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By Aldred S. Warthin, M. D.,
ANN ARBOR, MICHIGAN.

Mr. Chairman and Gentlemen: I think that it is unfortunate that syphilis has come to be regarded chiefly as a dermatologic affection. The prominence in the skin and mucous membranes of the earliest clinical manifestations of this generalized infection is, of course, responsible for the prevailing attitude of mind towards this disease. Such a conception, however, clouds the pathologic, clinical and prognostic understanding of syphilis in its broader and more important relations. There is no infection which is so constitutional or generalized as syphilis; there is no other one of the most important human infections, that, in its later stages is more "internal" and less dermatologic a disease than syphilis. But as the result of the prevailing clinical conception of this infection, what happens? The patient who contracts syphilis and develops a local lesion, followed by cutaneous and mucous- membrane manifestations is treated from the dermatologic standpoint; and after several days, weeks, or months of treatment —more or less, usually less—the clinical symptoms, that is, the dermatologic, usually disappear. With the disappearance of these more obvious phenomena of a generalized infection, a disappearance that takes place frequently as rapidly in untreated cases as in those treated, the patient usually considers himself cured and disappears from the observation of the dermatologist. What becomes of him? After a time, within a period usually of one to twenty-five years, this patient reappears, but where? Usually not in the clinic of syphilology and dermatology, but elsewhere!

He usually appears in the Clinic of Internal Medicine, as a case of vague cardiac disturbance, myocardial insufficiency, more or less well-marked symptoms of angina, arteriosclerosis, aortic disease, or aneurism; as a case of nephritis, diabetes or hepatitis; he may appear in the gastro-intestinal clinic with vague and usually wholly unrecognized syphilis of stomach or intestines; in the neurologic and psychopathic clinics he frequently turns up with vague and illy defined nervous symptoms, headaches, vertigo, psychoses, neurasthenia, the early and usually unrecognized symptoms of tabes or paresis, paralysis or insanity; in the eye clinic with impaired vision; in the ear clinic with auditory disturbances—in fact, in every other clinic but the dermatologic or syphilogic! Very often his symptoms are so vague and slight that the clinician can lay no definite finger upon them, and an accurate diagnosis is not made. The situation is further complicated by the ease with which syphilitics forget the fact of the early stage of their infection, and their fatuous certainty as to their cure, a state of mind into which they have usually been all-too-willingly led by the physician who saw them at the beginning of the infection.

Still more important in this connection

is that enormous body of individuals who do not know that they are syphilitic—the cases of non-venereal infection and the greater army of congenital syphilitics. The great majority of these never appear in the clinics of dermatology and syphilology; their clinical manifestations of syphilis are almost wholly *internal* and *visceral,* and they bring their conditions—often most difficult of diagnosis—to the internist, neurologist and psychiatrist, who very often do not discover the syphilitic nature of the affection.

Many of such patients come ultimately to autopsy, as the result of a premature death in the forties and fifties. At the autopsy table we find that these cases, entered in various clinics and treated as heart disease, kidney disease and other affections without recognition of the syphilitic origin, show a common pathology of a generalized latent infection, at one time more especially involving one organ or tissue, at another time another organ. These pathological lesions we now know to be due to the persistence of the spirochete pallida within the organs and tissues of the individual who has once contracted this disease. He is still a syphilitic—a spirochete carrier—and the pathological changes underlying his clinical manifestations are *lesions of syphilis.* Many of these pathologic changes can be recognized macroscopically as being essentially syphilitic, but in many cases they are so minute that their syphilitic nature can be demonstrated only by microscopical study.

The newer pathologic conceptions of syphilis have been made possible by the discovery of the spirochete pallida as the cause of syphilis. The presence of this organism in tissue-lesions must lead us to accept its etiologic relationship to those lesions, even if those lesions be different from those usually regarded as the essential histologic criteria of syphilis. The old pathologic criterion of syphilis was, of course, the gumma; and our pathologic diagnosis of syphilis rested upon the demonstration of the presence of gummatous lesions. Today, with our ability to demonstrate the spirochete in the tissues, we must accept a very much broader conception of the pathology of syphilitic infection. We know now that the gumma is not the chief histologic criterion of the presence of syphilis, but that it is relatively a rare occurrence in the pathologic processes of syphilis. The newer pathology of syphilis is built upon the occurrence of minute inflammatory processes leading to parenchymatous atrophy and connective-tissue proliferations, ultimately to fibrosis, and the demonstration of the presence of spirochete pallida in such lesions.

As a student in the old Allgemeines Krankenhaus in Vienna in the early nineties, there was indelibly fixed in my mind an observation made by Kolisko during the progress of an autopsy. Turning to me he said, "This is an old syphilitic. I can tell because of the toughness of his tissues." In a most surprising manner my studies of the spirochete pallida in the tissues have confirmed Kolisko's gross observations and the accuracy of his conclusions. The man who has latent syphilis for a number of years does develop all through his body minute inflammatory proliferations and infiltrations leading ultimately to fibrosis, so that his tissues do acquire a degree of firmness and toughness exceeding that of the non-syphilitic body. I do not know of any other chronic infection or intoxication that produces the same general pathologic picture seen in latent syphilis.

The material presented here today represents one hundred and sixty-five autopsies upon bodies showing the lesions of a generalized syphilitic infection. In but a small number of these was the existence of syphilis positively known clinically; the majority came from the clinic of internal medicine, as cases of nephritis, heart disease, etc., without suspicion of the true nature of the affection. In over fifty of these cases, without any clinical history of syphilitic infection or of symptoms of this disease, and with negative Wassermann reactions, the spirochetes of syphilis were demonstrated in the tissue-lesions. The general pathologic pictures in these undiagnosed cases is precisely the same as in the cases in which syphilis had been recognized. Several cases of paresis were included in this list. The general pathology of the cases of paresis is identical in kind with that found in the myocardial, nephritic, and other forms of latent syphilis. The pathology of these varied clinical types of latent syphilis varies only in localization and degree. With the aid of the lantern I am now going to show you the microscopical lesions of latent syphilis as they appear in the most important viscera. The syphilitic nature of these lesions has not hitherto been recognized, and the discovery of the relationship of the spirochete to these lesions has enormously broadened our conceptions of this disease.

My studies of the pathology of syphilis began about ten years ago with syphilis of the heart; and two years ago I presented before this Association in Cincinnati a report of some of the results of my study of myocardial syphilis. As you see in these slides syphilis of the myocardium is shown by a diffuse or patchy interstitial infiltration of plasma-cells and lymphocytes, with a slight fibroblastic proliferation leading ultimately to fibrosis. The fibroblastic proliferations are often somewhat myxomatous in character, giving a mucin test with mucin stains, such as Kresyl violet. In such myxomatous areas spirochetes are always present. The portions of the myocardium most frequently involved are the anterior wall of the left ventricle near the apex, the adjacent portion of the ventricular septum, and the posterior ventricular wall. Areas of plasma-cell infiltration and fibroblastic proliferation are found often around the coronary walls; the wall of the vessel itself is much less frequently involved. Spirochetes are found usually at some distance from the larger vessels. In many cases these lesions of the myocardium are so slight that it is hard to believe that they are clinically manifest; but in those cases in which the areas are larger, myocardial insufficiency results and brings the patients under the observation of the clinician. The lesions gradually become fibroid and hyaline. A hyaline area contains no spirochetes. It is a healed lesion; but spirochetes may be demonstrated in all cellular lesions. The presence of a cellular infiltration means that spirochetes are still present. Their number may be small, only a few found in each section, a small area of infiltration containing not more than ten to twenty organisms. We have accepted only typical spirochetes, typical in morphology and staining quality. Atypical forms are seen with these, but the significance of these is still unknown. The myocardial lesions occur in every case of syphilis, recognized or unrecognized, treated or untreated, cured or uncured. Active lesions have always been found when a sufficient time has been given to the search. Through a period of ten, fifteen, or twenty years, the progressive occurrence of such small inflammatory foci in the myocardium gradually brings the damage to the heart up to such a point that it becomes clinically manifest as a myocardial insufficiency. Every syphilitic has an impaired heart, and this impairment increases in degree as the years pass after his primary infection. It may be stated here that the demonstration of spirochetes in the myocardium of latent syphilis is by no means an easy matter. We have worked six weeks on one heart before we were successful in finding an active lesion with spirochetes present. We have used the Levaditi method exclusively, and consider it the only good method for the demonstration of spirochetes in tissues.

In every case of latent syphilis I have also found active lesions in the aorta. The gross appearance of aortic syphilis may or may not resemble those formerly taught as diagnostic of syphilitic aortitis. Cases in which the old classical picture of syphilitic aortitis is seen in the gross always show active lesions in abundance microscopically, but other cases in which the aorta presents the typical picture of a senile atherosclerosis may also show microscopically active lesions of syphilis and spirochetes. I have been obliged to change my teaching of the gross pathology of syphilis of the aorta. The microscopic findings are the only criterion of the presence of syphilitic lesions in the aorta wall. The active lesions of syphilitic aortitis in the adult are always in the adventitia and media, never in the intima. Around the veins and small arteries of the vasa vasorum there is the same slight plasma-cell and lymphocyte infiltration as seen in the myocardium. The process extends along these vessels into the media, with gradual obliteration of the arterioles. Degeneration of the intima with fibrosis, hyaline change, atheroma, calcification, etc., follow or accompany these changes, and the picture of artherosclerosis is gradually produced. Spirochetes should be sought in the small areas of infiltration about the veins of the vasa vasorum in the adventitia and outer part of the media. They occur in smaller numbers and therefore must be sought for with greater patience than in the case of the myocardium. I have never found them in the intima of the aorta in acquired syphilis, although in congenital syphilis localization of spirochetes in the intima are common, giving rise to localized proliferations of the intimal tissues.

Likewise in all of our cases of latent syphilis the pancreas shows a more or less marked fibrosis. Either a diffuse or patchy character of these lesions is very characteristic, normal lobules alternating with those showing most marked changes. With the fibrosis there occur the same small areas of plasma-cell and lymphocyte infiltration found in the heart and aorta. These may be either interlobular or intralobular. An apparent decrease in the number of islands of Langerhans occurs in all, while in many cases many islands are fibroid or hyaline. The lesions may be as severe in the non-diabetic cases as in the diabetic. Associated with the areas of inflammatory infiltration and proliferation striking pictures of regenerating parenchyma are found, consisting of newly formed acini arising from the ducts. Many of these formations suggest newly developed islands, but I am convinced that they do not represent these, but are small lobules of regenerating acini. The pictures in Opie's article on the pancreas in the Osler-McCrae System represent these regenerating acini and not islands. The syphilitic nature of the infiltrations and proliferations in the pancreas have been positively shown to be associated with the presence of the spirochete; and in those cases in which we have not looked for the organism precisely the same histologic changes exist. Opie says that syphilis of the pancreas is one of the rarest affections. I think we must change our views concerning this. I believe that syphilitic lesions occur in the pancreas in every case of syphilis, but these lesions are not gummas; they are mild chronic inflammations that may or may not cause a clinical pancreatic insufficiency.

Similar infiltrations of plasma-cells with slight fibroblastic proliferation occur in the liver, around the portal vessels; in the capsule and medulla of the adrenals; in the testis, with atrophy of the germinal epithelium and a slowly progressive hyaline fibrosis of the tubules; in the adventitia, and perivascular tissues of the mesenteric and prevertebral blood-vessels; in the meninges, in the brain and cord, in the intestinal and stomach wall—in fact, around any blood-vessel anywhere in the body there may be localizations of spirochetes with the production of these small inflammatory lesions. These lesions are, I believe, sufficiently characteristic to enable a diagnosis of syphilis to be made from the histologic picture alone.

The unfortunate individual who becomes infected with syphilis is a germ-carrier for the remaining years of his life. In the great majority of cases syphilis tends to become a very mild latent infection that often never again becomes of clinical importance, until the slowly progressive atrophy and fibrosis in an organ like the heart cause a functional incapacity that makes the disease manifest again — not as syphilis in the dermatologic sense—but as an internal affection, heart-disease, etc., as the case may be. And there is always this chance—this sword hanging over the latent syphilitic—something may happen to him that lowers his resistance, other infections, fatigue, intoxications, etc., and the latent syphilis renews its virulence.

It was a frequent remark of Kaposi in the old Dermatologic Clinic in Vienna, that "Syphilis is 75 per cent. of dermatology, and more than 50 per cent. of internal medicine." Today the truth of such a clinical observation is brought home to us by this newer pathology of latent syphilis, and I believe that internal medicine will in the near future again establish its proprietary right and interest in syphilis, for *latent syphilis is an internal disease.*

[NOTE.—The fact that this talk was given as a lantern-slide demonstration may serve to explain its somewhat sketchy character.]

A STUDY OF THE LIPIN CONTENT OF THE LIVER IN TWO CASES OF DYSPITUITARISM

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A STUDY OF THE LIPIN CONTENT OF THE LIVER IN TWO CASES OF DYSPITUITARISM*

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THE question of the fat-content of the various organs and tissues, in normal and in pathologic conditions, has been the subject of much discussion and research during the last decade. As the result of numerous investigations we know today that the majority of the tissues and all of the organs of the body contain fat under normal conditions. As regards the presence of fat normally in the hematopoietic organs there is still some conflict of opinion; but in certain pathological conditions these organs show marked accumulations of lipoid bodies showing that they must bear some important relation to certain forms or phases of fat-metabolism, at least. Great interest has been aroused by the discovery of the important part played by the lipoid bodies in various pathologic processes, and lipoid cells (cells with large amount of pale, vacuolated, foamy, reticulated cytoplasm and small, deeply staining eccentrically placed nuclei) are at the present time attracting much attention in pathologic histology. They have been found in many pathological processes; in inflammatory infiltrations, particularly lymphoid areas, in chronic aortitis, appendicitis, salpingitis, pyelitis, old ovarian abscesses, chronic mastitis, chronic cholangitis, prostatitis, chronic nephritis, actinomycotic abscesses, chronic granulation tissue, leprosy, rhinoscleroma, chorioid plexus, adrenals, neoplasms, etc. The xanthoma and pseudoxanthoma cells are lipoid cells. As to the histologic origin of the lipoid cells there has been much discussion; they are probably fibroblastic (reticulo-endothelial) cells in a state of lipoid infiltration (lipoid macrophages).

The chemical nature of the lipoid bodies represents still an almost unknown field. The school of Aschoff divides them into three groups, *glycerin-esters, cholesterin-esters,* and *lipoids* in a narrower sense (phosphatid, cerebrosid, fatty acids, and soaps). Mixtures of these substances, particularly of cholesterinesters and lipoids, are not rare. Histologically the lipoids may be demonstrated by staining with osmic acid, Sudan III, Scharlach R, Neutral red, Nile blue; by the methods of Smith-Dietrich, Fischler, and Ciaccio, and by polarized light. The cholesterol lipoids are doubly refractive (anisotropic) and stain less black with osmic acid, and more yellow or brownish with Sudan III and Scarlet R than do the glycerin-esters.

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*From the Pathological Laboratory of the University of Michigan.

Aschoff regards cholesterol-ester infiltration as a sign of chronic inflammation or of a chronic disturbance of metabolism. According to his views, in conditions, such as glycosuria, pentosuria, and chronic icterus, in which cholesterin-esters are present in abundance in the blood-plasma (cholesterinæmia) the cholesterin-esters are taken up by the cells (anisotropic fatty infiltration). However, Aschoff's views are not generally accepted, and by some writers are regarded as premature.

Our conceptions of the lipin metabolism of the body have recently been greatly widened by the discovery that lipoid bodies accumulate in the spleen and blood-forming organs in certain pathologic conditions, notably diabetic lipemia and Gaucher's disease. In 1903, Fischer noted in a case of lipemia that the spleen was hyperplastic and showed a diffuse infiltration of fat-droplets. Not until 1912 was a similar observation recorded when W. H. Schultze reported a case of diabetic lipemia in which the spleen showed almost complete replacement of the pulp with large, pale, vacuolated cells containing a lipoid substance probably closely related to cholesterol. Comparing his material with that from two cases of Gaucher's disease he concluded that the pale vacuolated cells in the latter affection were also filled with a lipoid substance and identical with the cells of his case. Brill and Mandlebaum, in 1913, were unable to demonstrate the presence of lipoids in the spleen in a case of Gaucher's disease, but their examination does not appear to have been complete. Lutz, in 1914, reported two cases of large-celled hyperplasia of the spleen pulp in diabetic lipemia, showing that his cases were similar to the one of Schultze; and that the large, pale, vacuolated cells were identical with those seen in the spleen in Gaucher's disease, but that the identity of the lipoid-containing cells did not prove that the two processes were identical. Sapegno has also reported two cases of Gaucher's disease, concluding that the characteristic large pale cells show a deposit of lipoids, and are similar to the cells found in the spleen in diabetic lipemia. He also refers to a case of obstructive jaundice observed by Kramer in which masses of lipoid cells were found in Glisson's capsule of the liver and in the splenic trabeculæ.

Following these observations Anitschkow produced in rabbits by prolonged feeding of cholesterol the same picture of large pale vacuolated cells (cholesterol steatosis) in the spleen, lymph nodes and bone marrow as that seen in Gaucher's disease and diabetic lipemia. In 1916, Wahl and Richardson reported a study of Gaucher's disease in an infant eleven months old. The spleen, liver, and lymph nodes presented the usual picture of Gaucher's disease, but in addition the medulla of both adrenals was almost completely replaced by clusters of large pale vacuolated cells. Similar cells were found in the intestines, Peyer's patches, thymus, and adventitia of some of the smaller vessels. A thorough chemical and histological study was made of this case; and the writers conclude that Gaucher's disease is due to a disturbance of lipoid and fat metabolism resulting in the accumulation of lipoid substances in the cytoplasm of large pale cells that are chiefly reticulo-endothelial cells of the spleen, lymph-nodes, bone marrow, liver, Kupffer stellate cells, etc. These cells are concerned in the metabolism of the fats and lipoids and comprise the "endothelial-Stoffwechsel-apparate." In advanced cases specific parenchymal cells also take up the lipoids. There is not only a marked increase in the lipin content, but a marked alteration in the normal relations of the lipins. The fixed fats are greatly reduced, and the lipoids, such as lecithin and cholesterol, greatly increased. A lecithin-like body predominated in their case. Gaucher's disease therefore must be classed with the group of xanthelasmic conditions which are characterized by a more or less diffuse accumulation of lipoids in reticulo-endothelial or fibroblastic cells in one or more organs. It is a more diffuse and widespread involvement of the "endothelial-Stoffwechselapparate" than the cases of large-celled hyperplasia of the spleen seen in diabetic lipemia.

A clinical and pathological study of two cases of Gaucher's disease in infants reported by Knox, Wahl and Schmeisser, in 1916, includes the case given above and the sister of that case, aged fifteen months. The pathological findings in the second case were similar to those of the first; the essential feature being the occurrence, particularly in the hematopoietic system, of large pale vacuolated cells containing a peculiar refractive substance having the chemical and staining properties of lipoid material. These writers regard their two cases as identical with the cases reported as Gaucher's disease, and conclude that this affection "is not primarily a disease of the spleen, or of any other organ, or set of organs, but is a generalized process due to a disturbance in fat metabolism, manifesting itself by lipoid metamorphosis, that is, by the more or less diffuse accumulation of lipoid material in many cells with the formation of the characteristic large pale cells. This process is most prominent in the hematopoietic system, especially in the spleen and lymph nodes, organs that are said to play a not unimportant role in abnormal fat metabolism."

If these conclusions as to the nature of Gaucher's disease are correct, an entirely new field of pathologic metabolism has been opened up, aside from the elucidation of the nature of the mysterious large pale cell characteristic of this process. As our knowledge of the lipoid bodies is so incomplete any new light thrown upon fat and lipoid metabolism becomes particularly valuable at this stage. Through the study of such pathologic disturbances of lipoid metabolism we may gain important knowledge of the normal metabolism. Some progress into this field has already been made. The part played by the adrenals and spleen in lipoid metabolism has already been pointed out by several writers. Krylow believes that the adrenal cortex regulates lipoid metabolism, and that any insufficiency on its part would lead to an accumulation of lipoids in other parts of the body. Chalatow, Soper, Kusunoki, and others have pointed out the importance of the role of the spleen in lipoid metabolism. Soper holds that the spleen's apparent large part in this is due to its extensive reticulo-endothelial system. The liver also plays a very important part in the regulation of cholesterin metabolism. By some writers it is placed between the adrenals and the spleen and endothelial apparatus in its relative importance in so far as this function is concerned. Other organs and tissues (sex-glands, panniculus, etc.) may play an important role in the maintenance of cholesterol equilibrium, but we as yet have no definite knowledge of such metabolic processes. Increase of cholesterin in the blood has been noted in pregnancy. Injection of cholesterin emulsions in tumor-grafted rats has appeared to increase the rate of tumor-growth (Burnett and Robertson). Luden has found high cholesterin values in patients suffering from malignant disease, and on very insufficient grounds has advanced the hypothesis that cholesterin retention due to insufficient conversion or deficient elimination may be a primary factor in the etiology of malignant disease.

All forms of disturbances of fat metabolism should be studied in the attempt to add knowledge to this subject, particularly those of a generalized character. I wish to present here such a study in a field as yet untouched, the marked disturbances of fat-metabolism occurring in hypophysis disease (dyspituitarism). Two autopsy cases of this condition showing the two stages of this affection, one of adolescent dystrophia adiposo-genitalis, the other of dyspituitarism in an adult following an acromegalic stage, have occurred in my service Both cases presented the striking obesity characterizing hypopituitarism. As far as I have been able to discover no studies have as yet been made of the character of the fat in this condition. Cushing, in his book on "The Pituitary and its Disorders" remarks (page 258) that "The adiposity of hypopituitarism is a generalized one—not limited solely to the panniculus—though its bedside recognition is necessarily restricted to the character of the subcutaneous disposal. The fat shows postmortem, certain peculiarities of color and consistency which suggest a different chemical composition from 'normal panniculus,' and is worthy of a differential analysis. It furthermore invades the organs, and in the liver particularly, there is often an extraordinary replacement of the cells by fat globules." In his description of the changes in the adrenals (page 281) he says: "As is true of the experimental states of hyperpituitarism [?], so in the clinical cases the adrenals which we have had an opportunity of studying histologically have shown an abnormal vacuolization (a lipoid change?) of the cells of the zona fasciculata of the cortex (Fig. 313)." In the legend of this figure the condition is correctly stated as hypopituitarism, evidently a typographical error in the text, and the adrenal pictured shows a condition of marked liposis.

CASE I.

H. F., Schoolboy, aged 18 years. American. Admitted to Neurologic Clinic (Dr. Camp), 1-16-12.

Chief Complaint.—Failing vision.

Family History.—Negative. Two brothers and two sisters, living and well.

Previous Personal History.—Has had measles and smallpox. No history of injury. No bad habits. Has had some headaches ever since he can remember. accompanied by nausea and occasional vomiting.

Present Trouble.—About one year ago the headaches became more severe and constant. He then had convulsions, and was unconscious for two weeks (with spasms during first week). No fever. Eyes began to fail two years ago. Since the attack of unconsciousness his headaches have been less severe. At present he complains chiefly of a difficulty in vision and constant sleepiness. Is in the 11th grade at school. Seems as bright mentally as the other pupils.

PHYSICAL EXAMINATION.—Very obese boy. Height 4 ft., 10½ in. Weight, 120¾ lbs. . Panniculus hangs in long folds from breast and abdomen. Feminine type. Well developed mammæ. Face rounded and full. Skin of good color. No axillary hair; very little pubic hair. Neck very short with adipose collar. Thyroid not enlarged. Genitalia very poorly developed, hardly visible. Right testicle undescended. Hands and feet short and stubby. No enlarged glands. Heart sounds very faint and irregular. Mentality good. Facial expression drowsy. Occasionally a choreiform movement in the extremities. Can count fingers at about five feet. Reflexes diminished. Prickly sensations at times over the skin, particularly in thighs. Urine negative. R.b.c., 4,370,000; w.b.c., 12,050; hemoglobin 90. X-ray examination shows a dense mass about the size of a hazel-nut in the anterior portion of the sella. Ophthalmologic examination showed well-advanced optic atrophy. Blood-pressure 105.

Operated by Dr. Canfield 2-9-12. Took anesthetic badly. Route through the sphenoidal cells removing part of the floor just anterior to the anterior wall of the sella. Through the opening meninges and brain bulged. This was punctured and about two drams of blood and fluid escaped. Operation closed without removal of hypophyseal tumor. Patient recovered consciousness, and remained so for several hours without pain; then became delirious, with spasms of eyes and face, great restlessness. Temperature per rectum 104°. Became gradually semiconscious. No paralysis. No pain. Developed spasms before death at 6 A. M. next morning. The autopsy was made five hours after death.

AUTOPSY PROTOCOL.—EXTERNAL EXAMINATION.—Body of a very obese boy, apparently about ten to twelve years old. Length 150 cm. Somewhat feminine in type. Breasts very fat; no fluid can be expressed from them. Hands and feet short and thick. Abdomen above level of thorax, large folds of panniculus. Face has a rather stupid adenoid expression. Very fat and rounded. Marked fatty collar. Hair of head is abundant, but there are few axillary and pubic hairs; these are fine and light in color. Both testicles are in the small scrotum; they are about the size of those of a ten year old boy. Right one is smaller. Short retracted foreskin; glans normal. Mucoud secretion dripping from meatus. Panniculus throughout very thick and firm. No edema except slight over ankles. Muscles poorly developed. Rigor mortis only in muscles of jaw. Body is very warm, feels hot to the touch. Teeth negative. Nostrils are dilated, and contain clots of blood. Arms and legs show a number of bruises. Hypostasis is marked, purplish red. Sacrococcygeal dimple is very marked. Percussion of thymus region shows an increased area of dullness.

Spinal Cord.—Not removed.

Brain.—Scalp and periosteum negative. Skull-cap is thin, particularly over the vertex where there are well defined areas of deficient ossification, and also in the region of the fontanels. Dura is firmly adherent all over, and increased in thickness along the longitudinal sinus. Intracerebral pressure greatly increased. Meningeal and pial vessels are markedly congested. Meninges over frontal lobes are covered with fresh blood-clot; and there is an extravasation of blood through the subarachnoid space. On lifting the frontal lobes there is seen a large recent clot between the base and the optic nerves. Blood clots in left temporal and occipital regions. Brain is adherent to the cranial floor in the neighborhood of the hypophysis. On separating the attachments the softened brain substance in the neighborhood is much torn. It is discolored and partly necrotic and hemorrhagic. A large clot extends between the frontal lobes along the left anterior cerebral. The softening of the brain substance and hemorrhage are most marked in the neighborhood of the chiasm where the basal dura is torn and the floor of the skull penetrated by the operation anterior to the hypophysis. No trace of this organ is visible. The sella is not greatly enlarged and is filled with a projecting mulberry mass, very hard and giving a clear ringing sound when struck. In the floor of the cranium just anterior to the sella is a similar hard nodule the size of a peppercorn. From the hard mass in the sella an atypical softer tissue infiltrates the discolored and softened brain tissue lying above it. The basal arachnoid and pia are much thickened and covered with recent clots. Ventricles dilated, contain a blood-stained fluid. Pineal gland normal in size and appearance. Choroid plexus negative. Cerebral and cerebellar tissues soft, edematous and congested.

Main Section.—Abdominal panniculus 5 cm. thick; that over thorax is 3 cm. It differs in appearance from normal fat; when first cut into it is very glistening, translucent, very firm and is light buffy-yellow in color. The panniculus is very warm to the touch, steaming. On cooling it becomes more buff in color, opaque and very hard. The lobules are much larger than normal panniculus. The appearances suggest a myxedematous fat. The subserous panniculus is 3 cm. thick and of the same character. Omentum and epiploic appendages, mesentery and subserosa of bladder show similar thick deposit of fat. The abdominal and thoracic muscles are small and show abundant fatty infiltrations. No free fluid or gas in peritoneal cavity. Liver very large extending 3 f.b. below ensiform, and 2 f.b. below edge of ribs in right nipple line. Spleen not enlarged. Diaphragm 5th rib on left; 4th on right.

Thorax.—No fluid or gas in thoracic cavity. Lungs free. Apex of heart in 4th intercostal space, left parasternal line. Mediastinal fat very abundant. Thymic region filled with a large pink, two-lobed thymus, the left one extending over left ventricle to apex, the right one covering the right auricle. The upper boundary of the lobes touches the thyroid. Pericardium normal. Heart normal size; undersized if amount of panniculus is taken into account. This is very abundant. Right ventricle contains large red and white clot. Left ventricular wall is 10 mm. thick. Mitral flaps and orifice negative. Pulmonary artery and aorta negative. Foramen ovale and ductus arteriosus closed. The lungs show marked congestion and numerous small hemorrhages. The intima of the ascending portion of the aorta shows patches of fatty degeneration.

Neck Organs.—Thyroid is small. On section shows but little colloid, resembles foetal thyroid. Homogeneous surface. Four brownish-pink parathyroids. Not enlarged. Cervical glands not enlarged.

Abdomen.—Spleen weighs 50 gms. Soft. Capsule negative. Follicles numerous, large. Cut surface shagreened. Large intestine distended; unusually large; otherwise negative. Stomach negative. Pancreas normal in size and consistency. Much fat about it. Both adrenals are large, absolutely and in proportion to size of kidneys. Cortex yellow, medulla hypoplastic, much fat about both adrenals. Kidneys have enormous fatty capsules. Fibrous capsules strip easily. Fetal lobulations well preserved. On section kidneys show marked congestion. Pelvic fat much increased. Liver weight 1030 gm., capsule negative. Surface mottled, yellowish and red, with fatty shine. Lobules not distinct. Mesentery very fat. Mesenteric and retroperitoneal nodes not enlarged.

Genitalia.—The testes are surrounded by a fatty sheath. On section they appear as undeveloped infantile testes. Prostate cannot be felt or seen. Seminal vesicles not developed. Other organs negative.

MICROSCOPICAL EXAMINATION.—*Tumor of Hypophysis Region.*—Presents the appearance of an adamantino-carcinoma with hyaline and calcareous masses of a dentine-like substance arranged in mulberry masses or agglomerations of rounded concretions. These are formed by the hyaline transformation of cords and strands of large squamous prickle-cells. Cords of these cells infiltrate the brain substance after the manner of a carcinoma; those in the brain for the greater part showed no calcification, and the cell-cords consists chiefly of a central hyaline mass around which cells with very large intercellular bridges or prickles are grouped showing the characteristic palisade arrangement at the periphery of the hyaline mass. Small cords show no hyaline change. The brain tissue about the tumor-cords shows atrophy with marked gliosis, and occasional cellular infiltration. A small area of hypophysis tissue corresponding in structure to the pons anterior was found showing the same adamantinoma infiltration.

Thyroid.—Many follicles contain a thin colloid; but the majority contain none. The organ closely resembles the fetal thyroid.

Parathyroids.—These were hypoplastic and showed fatty infiltration.

Thymus.—Hyperplasia of the medulla; atrophy of cortex.

Heart.—Fatty infiltration.

Aorta.—Diffuse fatty degeneration of the intima, with small raised patches of lipoid cells resembling those of Gaucher's disease.

Lungs.—Marked congestion and edema; hemorrhages; acute purulent bronchitis and bronchopneumonia.

Spleen.—Marked congestion. Large follicles with lymphoid exhaustion. Sclerotic arterioles. Scattered lipoid cells, not numerous.

Stomach.—Negative.

Intestines.—Excessive mucus formation.

Pancreas.—No changes noted.

Mesenteric and Retroperitoneal Nodes.—Lymphoid exhaustion.

Adrenals.—Abundant chromaffinic cells. Hypoplastic medulla; cortex hypertrophic with marked but irregular liposis, involving in some regions the glomerular zone, in others the fascicular. Marked hypertrophy of some of the fascicular cords.

Kidneys.—Cloudy swelling and congestion. Numerous glomerular scars. Scattered lipoid cells in lymphatics about large veins.

Testes.—Infantile in type, with vacuolation of germinal cells. Interstitial cells hypoplastic.

Liver and Panniculus.—Will be described below with that of Case II.

PATHOLOGICAL DIAGNOSIS.—Infantilism, dyspituitarism adiposo-genitalis; adamantino-carcinoma of hypophysis; hyperplastic thymus; lymphatic constitution; general lipomatosis (liposis) most marked in liver (cholesterol steatosis); intraperipheral zonal necrosis of liver; hypoplasia of thyroid and adrenals; post-operative hemorrhage and operative trauma at base of brain; acute purulent bronchopneumonia (aspiration).

CASE II.

J. B. M., age 29 years; sailor by occupation. By birth American. Admitted to Neurologic Clinic (Dr. Camp), March 9, 1912.

CHIEF COMPLAINT.—Disturbances of vision, staggering, mental disturbances.

FAMILY HISTORY.—Negative. No case of tuberculosis, cancer, or nervous disease.

PERSONAL HISTORY.—Always well until present trouble began. Mentality always good. Has lived an out-of-doors life. Three years ago began to have violent headaches every few days, lasting 1-2 days and followed by vomiting. After two years these stopped suddenly. At this time he began to complain "of not feeling well," but had no well-defined symptoms. Slept a great deal, all night and during the day except when wakened for meals. Would fall asleep on duty. Suddenly noticed a peculiar tendency to lean to the left when walking, as well as a peculiar manner of carrying left arm. Developed hoarseness and a hesitating slow speech, with difficulty in making himself understood. Lost interest in everything, and avoided particularly reaching for things, asking others to do this for him. Lost his skill in marksmanship and his interest in sports. The difficulty in walking has steadily increased, as have choking spells induced by eating. His sister has noticed nothing strange about his mentality except a slight childishness. During the last year he has had five attacks of dyspnea, hard chills, hands drawn up, side of face drawn up, and fever running as high as 103.5°, followed by vomiting. Cannot walk well after attacks, and has fallen several times. At the present time he has to be dressed and fed. Cannot walk out alone. Smokes excessively; denies alcoholism and venereal disease. No note made of sexual state. Last May was examined by Dr. Parker in Detroit who found ½ vision in each eye. Was x-rayed at this time.

PHYSICAL EXAMINATION.—(March 11, 1912, by Dr. Camp). Large build, well nourished, wears a No. 8 shoe. Hands are large, but patient says they have always been so. Head is fairly large; normal shape. No acromegalic jaw. Thyroid not enlarged. Mentality seems fairly clear. Tendency to senseless jokes. Slight clouding of consciousness; memory is defective except for more recent events. No delusions; no mental retardation. Replies are prompt, although speech is slow. Left pupil reacts to light; right does not. Neither pupil reacts to accommodation. Some defect in lateral motion, particularly to the right. Eyeballs do not converge. Temporal hemianopsia in left eye; in the right eye some contraction of the visual fields in all directions, but no distinct hemianopsia. Palpebral fissure a little wider on left side than on right. Right side of face drawn up distinctly better than left. Tongue straight, no tremor, no atrophy. No ataxia; no intention tremor; no hemiasynergia in hands. Slight staggering gait with eyes closed. Sensory tests normal. Reflexes prompt and equal. Examination of heart, lungs and abdominal organs negative. Urine negative. Lumbar juncture negative. Wassermann negative. Patient was examined again on June 29, 1912, by Dr. Camp. Condition about the same. Returned December 2, 1912. Examination by Dr. Camp. Had severe headaches after leaving the hospital in June;

none until yesterday when he had a severe attack with dizziness. Fell heavily, but was not unconscious. Says that he was paralyzed on the left side four months previously. Symptoms about the same as before. Blood and spinal fluid gave negative Wassermann. Headaches increased. Patient feels "all in." Examination by Dr. Canfield revealed the presence of a nasal tumor. Operated on December 21 by Dr. Canfield. Submucous resection of the septum showed a tumor mass extending from the sphenoid cavities from regions back of the sphenoid down into the septum. The tumor was very soft, dark grayish in color, and flecked with white spots. Microscopical examination of this in our laboratory showed the neoplasm to be a large round cell sarcoma containing numerous calcareous concretions (psammoma). Regarded as probably primary in basal meninges.

After the operation condition continued unchanged (headache, sleepiness, etc.). Temperature rose to 105° the day after the operation. On January 16th he complained of more or less constant pain through temples. Seen at intervals of several weeks. Irrational at times. By April 9, 1913, enlargement of hands was notable. His sister said that this had occurred during the last few weeks. Sleepiness increased. By May 19 his face and head looked distinctly larger; appearance of hands typically acromegalic. Feet not grossly enlarged. Chief complaint still headache and "sour stomach." Anxious to have another operation because of "untold agony" in head. Glucose (100 gms.) test negative. Acromegalic condition increased, slowly until January, 1914, when his sister noticed that his shoes were looser. Complained at this time of chilliness; skin of hands mottled and discolored. Tonic convulsive movements in upper extremities. Temperature rises to about 103° after chill. Subcutaneous panniculus all over the body increased. Secondary type of optic atrophy in right eye. Fundus of left is more congested than right. Headaches have ceased. No note of sexual state occurs in the history. Patient showed gradual cessation and subsidence of the acromegalic condition with increasing symptoms of hypopituitarism (increase of panniculus, etc.) until his death on April 15, 1914, at 7:50 A. M. Autopsy at 10 A. M.

AUTOPSY PROTOCOL.—Body large; masculine type; length 175 cm. Acromegalic facies and hands. Obese; panniculus abundant all over body. Body and head hair abundant. Genitalia well-developed; testicles soft and flabby. Body very warm; axillary temperature 99°, rectal 104°. No rigor mortis. Moderate purplish hypostasis.

Spinal Cord.—Not examined.

Head.—Scalp and periosteum negative. Skull-cap thickened; inner surface rough, gray, meningeal grooves prominent. No exostoses. Pacchionian depressions shallow. Diploe sclerosed. Dura not thickened but adherent throughout. No osteomata in dura.

On lifting and removing the brain a large soft tumor is found at the base, in the interpeduncular space, extending more into the base of the right cerebral hemisphere than on the left. Smaller lobulated masses are found about the periphery of the larger mass. The tumor has destroyed the right optic tract and displaces the 5th and succeeding cranial nerves backward. The third nerve appeared to pass through the tumor. The pons was compressed by the tumor to half its normal thickness. On the right the growth extended into the right temporosphenoidal lobe by two finger-like projections, one in the region of the right lenticular body, the other into the third ventricle. The internal capsule was compressed between them. Tumor was reddish, soft, well encapsulated toward the brain substance, but ragged and torn below where it had been separated from the tumor mass extending through the floor of the skull into the retropharynx. Anterior to the sella there was an opening about the size of a silver dollar through which a tumor-mass about the size of a tennis ball extended into the nasopharynx. Base of skull about the opening was soft, necrotic and infiltrated with extensions of the growth. The anterior portion of the sella was destroyed, and no trace of hypophysis tissue could be made out, the entire organ apparently having been destroyed by the growth.

Main Section.—Abdominal panniculus is 5 cm. thick, thoracic 3 cm. The fat is in large coarse lobules, unlike normal fat, pale lemon-buff in color, firm, translucent and shining; but becoming darker and opaque on cooling. The panniculus is very warm to the touch. Omentum is rich in fat of the same type; likewise the epiploic appendages and mesentery. Abdominal organs very hot, almost bloodless. Intra-abdominal temperature 107.1°. Tissues dry very quickly on exposure to air. No free fluid in cavity. Lower border of liver at ensiform in mid-line, a hand's breadth above the lower edge in right nipple line. Slight rigor mortis in abdominal muscles. Diaphragm at 5th ribs.

Thorax.—No fluid in thorax. Apex in left parasternal line behind 5th rib. Lungs meet anteriorly above. No pleural adhesions. Fat tissue in anterior mediastinum very abundant, of same appearance as the panniculus. Large lobules of thymic fat in which remains of thymus are present. On section thymic fat is diffusely pink. Heart is negative, save for a dilatation of the right side, an adherent thrombus in the right auricular appendage, increased subpericardial fat, brown atrophy of muscle and a thickening of the endocardium of the left auricle. Aorta showed early sclerosis in the ascending part of the arch. Lungs show passive congestion. Entire lower lobe of right lung is airless, solid, early stage of red hepatization.

Mouth and Neck.—Hyperkeratosis of tongue (brown hairy tongue). Papillæ at root hyperplastic. Larynx, trachea and esophagus negative. Thyroid is slightly larger than normal, colloid is not diminished. Parathyroids hyperplastic, 8 mm. in diameter, purplish in color. Cervical hemolymph nodes hyperplastic.

Abdomen.—Spleen weighs 120 gms. Small, soft, shows few follicles on section.

Stomach and Intestines.—Dilated, otherwise negative.

Pancreas.—Fatty infiltration of tail. Soft.

Liver.—Very hot to the touch. Clinical thermometer inserted showed five hours after death a temperature of 108°. Small in size, weighs 1730 gms.; sharp edges; mottled surface; yellowish red; opaque fatty shine.

Mesentery is very rich in fat, arrayed in coarse lobules, lemon-yellow color, appearance same as that of panniculi. Fat changes color on exposure to air, becoming a diffuse pink in many areas, giving it a peculiar mottled appearance.

Adrenals are very large, 8 cm. long, 5 cm. broad, and 4 mm. thick. Surrounded by dense masses of fat and old fibrous adhesions.

Kidneys have very large fatty capsules. Fibrous capsule strips easily on the left, somewhat adherent on the right. On section kidneys show slight atrophy and congestion. Retroperitoneal lymph nodes atrophic, show fatty infiltration. Thoracic and abdominal muscles show fatty infiltrations.

Pelvis.—Penis negative. Left testis rather pale. No increase of stroma visible to the naked eye. Right testis pale, soft. Prostate smaller than normal, congested. Seminal vesicles very much dilated with a thin watery fluid. Walls negative. Bladder and rectum negative.

Microscopical Examination.—Sections of neoplasm from base of brain and nasopharynx show it to be a round cell angiosarcoma with numerous psammoma concretions scattered through it. It bears no resemblance to the hypophyseal struma. In the sella turcica region there were found areas in a number of sections of a typical hypophysis adenoma or struma (chromophobe type) infiltrated, compressed and destroyed by the sarcoma. The appearances lead me to believe that a typical acromegalic hypophyseal struma has been either the seat of a malignant change, or what is more likely has been destroyed for the greater part by a sarcoma arising primarily in the basal meninges or in the floor of the skull. The penetration of the latter, the early growth downward into the nasopharynx and septum support the latter view. The neighboring brain structures show pressure atrophy and necrosis, gliosis and sarcoma infiltrations.

Tongue.—Hyperkeratosis.

Thyroid.—Colloid hyperplasia.

Parathyroids.—Hyperplasia.

Cervical Lymph Nodes.—Marked lymphoid hyperplasia and congestion. Large germ centers with exhaustion of the lymphocytes. Sinuses crowded with macrophages, many of these are hemophages containing red cells or pigment, many of them are filled with fine fat droplets (lipoid cells). Apparent very active hemolysis.

Lungs.—Acute hypostatic pneumonia. Edema and chronic passive congestion.

Heart.—Brown atrophy, fibrosis, fatty infiltration and degeneration; slight cloudy swelling.

Thymus.—Remains of thymus in fat tissue showing newly-formed cords of lymphoid tissue along lymphatics distended with macrophages and hemophages. Hassall's corpuscles small and few.

Spleen.—Chronic passive congestion, atrophy. Few scattered lipoid cells. Numerous hemophages.

Stomach and Intestines.—Acute catarrh. Appendix contains fecal concretion. Old appendicitis.

Pancreas.—Fatty infiltration. Very large fat cells with greenish coloration, showing mixture of lipoids. Hypertrophic islands of Langerhans. Hyaline substance in many acini.

Liver.—See below.

Adrenals.—Marked hypoplasia of medulla. Small amount of chromaffinic tissue. Practically the entire cortex shows a marked liposis of the parenchymatous cells. The liposis is most marked in the glomerular and fascicular zones. Hypertrophic fascicular cords are also numerous. (See further below.)

Kidneys.—Cloudy swelling and fatty degeneration of the tubular epithelium.

Areas of chronic and subacute nephritis. Numerous casts. Lipoidosis of tubular cells.

Aorta.—Early sclerosis. Fatty degeneration of intima. Small elevations made up of collections of lipoid cells in intima.

Mesenteric and Retroperitoneal Lymph Nodes.—Hyperplasia, lymphoid exhaustion, sinus catarrh, great numbers of macrophages and hemophages. New formation of lymphoid tissue throughout mesenteric and retroperitoneal fat. Many lipoid cells.

Hemolymph Nodes.—Hyperplasia. Sinuses crowded with hemophages containing blood cells and pigment. Scattered lipoid cells.

Testes.—Aspermatogenesis. Stroma increased. Basement membranes thickened. Fatty degeneration (liposis) of germinal epithelium.

Prostate.—Moderate glandular hyperplasia.

Seminal Vesicles.—Negative.

PATHOLOGICAL DIAGNOSIS.—Hypopituitarism following acromegaly (sarcoma replacing hypophysis struma); sarcomatous infiltration of brain, base of skull, nasal and pharyngeal cavities; general obesity (general liposis); cholesterol steatosis of liver and adrenals; intraperipheral zonal liver-necroses; postmortem hyperpyrexia; hyperplasia of adrenal cortex, hypoplasia of medulla; hyperplasia of lymphatic and hemolymph nodes with hemolysis; hypertrophy of islands of Langerhans; persistent thymus; lymphoid exhaustion of germ-centers; subacute parenchymatous degenerative nephritis; acute hypostatic pneumonia; acute gastrointestinal catarrh; hyperkeratosis of tongue.

ANALYSIS OF CASES.

These two cases of hypophysis disease present several striking features in common. They are both examples of hypopituitarism, Case I, with deficient hypophysis secretion from the beginning; Case II, with an earlier stage of hyperpituitarism (acromegaly) succeeded by a period of hypopituitarism following the destruction of the primary hypophysis adenoma (struma). Although, as Cushing has strongly emphasized, cases of hyperpituitarism sooner or later pass into a second stage of hypopituitarism, it seems reasonable to suppose that the transformation in this case is explainable upon the apparent grounds found. Leaving the hypophyseal features of both cases and the acromegalic symptoms of Case II out of the question, the general picture in both cases is the same: a marked obesity or liposis involving all organs, particularly the panniculi, liver and adrenals, with scattered lipoid cells elsewhere. The atypical character of this fat was shown best in the liver and adrenals, and it was most thoroughly studied in the former organ.

LIVER CHANGES IN CASES I AND II.—Both livers show identical changes, perhaps more marked in Case I, although portions of the liver in Case II show as marked changes as any in the liver of Case I. These changes will now be described in detail.

Hematoxylin and Eosin Preparations.—Sections from blocks imbedded in paraffin and stained with hematoxylin and eosin give on first glance the picture of a fatty liver in which the processes of fatty infiltration and fatty degeneration are combined. The lobules are smaller than normal. The cells of the central liver-zone show numerous fine droplets or vaculations, giving the cell the characteristic "ground-glass" appearance. Through the intermediate and peripheral zones large fat droplets appear, not regularly as in an ordinary fatty liver, but arranged in more or less well defined groups. They are, however, most numerous toward the outer portion of the intermediate zone, and not at the periphery of the lobule. Groups of such large vacuoles occur also in the central zone. Small fat droplets are found also in all of the liver cells except in certain peculiar zones or bands that run around the lobule in the inner portion of the peripheral zone. In these areas there are few fat droplets, the liver cells are small, granular, necrotic or replaced by a cellular fibroblastic area in which remains of liver cells can be made out. In a few lobules these fibroblastic zones touch the periportal islands, but usually a narrow zone of liver cells filled with fine fat granules separates this zone from the trabeculæ. This picture seems to me to be quite unique. I have never seen anything like it in any other liver but in these two cases of hypopituitarism. The periportal tissue is cellular and fibroblastic, frequently showing newly formed bile ducts in numbers. The appearances are those of an early stage of a peculiar form of cirrhosis. It shows more distinctly in the H. and E. preparations of Case I than of Case II; but the peculiarity of this change is best revealed in the sections stained with Sudan III and Scharlach R. and counterstained liver with hemalum. The protoplasm of the outermost cords of cells stains most heavily and has the smallest number of fat droplets. The veins are dilated, but the intralobular

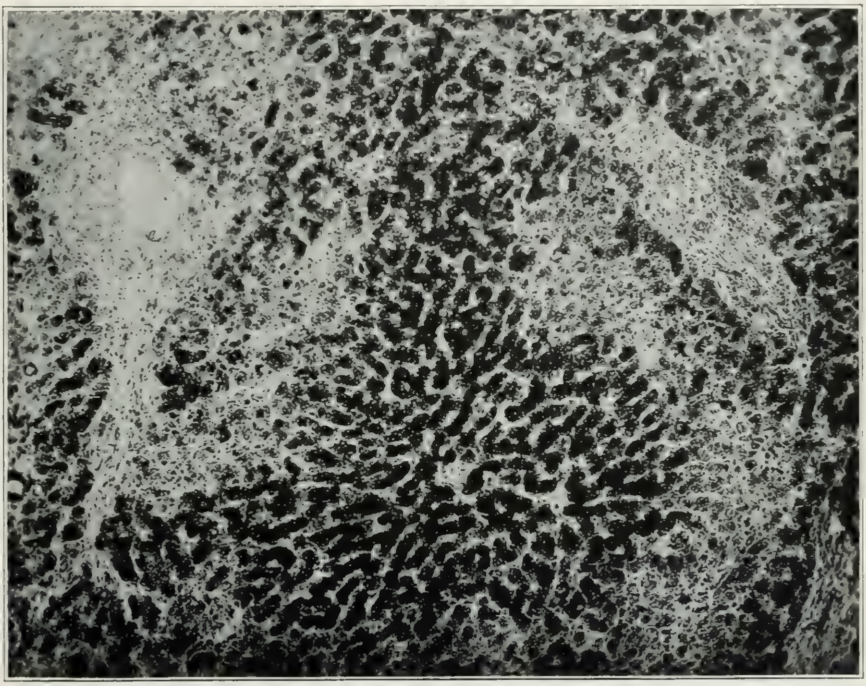

Fig. 1.—Cross-section of liver lobule from liver of Case I. Frozen section, Sudan III and hemalum stain. Central zone and portion of mid-zone and narrow border of peripheral zone show liver-cells filled with minute anisotropic droplets staining deep brownish red, with larger scattered isotropic droplets staining deep yellow-red. Inner portion of peripheral and outer portion of mid-zone show peculiar necrosis with fibroblastic proliferation (intraperipheral necrosis and beginning cirrhosis).

capillaries only moderately so. There is no picture of nutmeg liver or central necrosis, the liver cells around the central veins staining as well as those in the periphery as far as the nuclei are concerned. There is no necrosis, and no pigmentation of the liver cells of the central zone. Iron tests were negative. No pigmented stellate cells were found. Bile-ducts showed no changes.

MICROCHEMICAL STUDY.

Osmic Acid.—In frozen sections treated with one per cent osmic acid, or in sections so treated after formol-fixation the fat content of the liver cells was more decidedly revealed. The small droplets in the central zone of the lobule stained a lighter gray than the large fat droplets scattered irregularly. Some of the droplets are not acted upon at all by the osmic acid or show only the slightest gray tint (cholesterol). The peculiar distribution of the fat in the two livers stands out very prominently in the osmic acid preparations. There appear in addition droplets of fat apparently in the lumina of the liver capillaries, and these were mistaken at first for free fat emboli in Case I. They are undoubtedly stellate endothelial cells showing a marked lipoidosis. These give a more gray color-reaction with the osmic. Osmic preparations of adrenals and aorta showed similar color reactions, a large part of the small droplets staining light gray. Sections of the panniculus stained deep brown black.

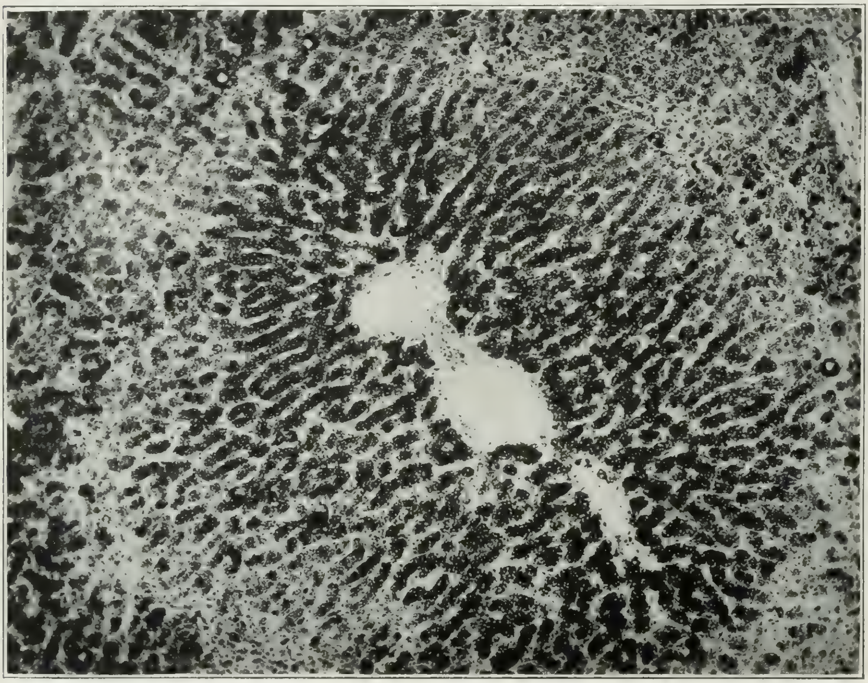

Fig. 2.—Cross-section of liver-lobule from liver of Case II. Frozen section, stained in Sudan III and hemalum. Central zone, greater portion of mid-zone and narrow outer portion of peripheral zone show liver-cells filled with fine anisotropic droplets staining deep brownish red, with scattered larger isotropic droplets staining deep yellow-red. Inner portion of peripheral zone and outer portion of mid-zone show the peculiar necrosis and early cirrhosis (intraperipheral necrosis).

Sudan III.—Beautiful preparations were obtained with frozen sections stained in an acetone solution of Sudan III and counter-stained with hemalum. The fine fat droplets in the central zone and throughout the liver-lobule stained a peculiar brownish-red, while the majority of the larger droplets stained an orange-red to brick red as does neutral fat (glycerin-esters). Other large droplets were light yellow or pale buff in color. Counterstaining with hemalum brought out the unique distribution of the fat in the liver-lobules. The fat-free areas or zones stand out in these preparations so strikingly and the cellular infiltration and proliferation is so prominently brought out that it is difficult to believe that one is looking at the same tissues seen in the paraffin-hematoxylin-eosin preparations. Occasional fat-droplets are found in these necrotic zones, and such appear to be chiefly in the stellate cells, although a few liver-cells containing large droplets occur also. The borders of these blue zones, as they appear in the hemalum preparations show a transition from liver-cells containing brownish red granules to cells containing fine brown granules. These brown granules are finer than the red ones and are scattered in the same manner through the cell. They do not give a hemosiderin reaction. Some liver-cells with red granules in one end and brown ones in the other are seen in the borders of these relatively fat-free zones. It is evident, however, that the lack of fat in these narrow zones is due chiefly to a necrosis or disappearance of the liver-cells in these areas, and to a replacement of these by a fibroblastic proliferation.

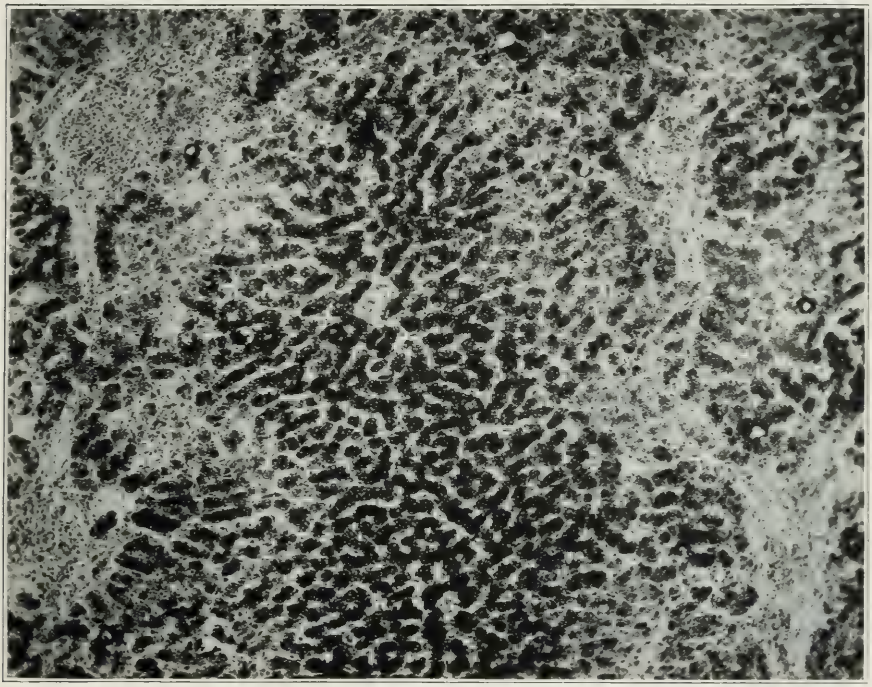

Fig. 3.—Tangential section of liver-lobules from liver of Case I. Frozen section, Scharlach R and hemalum stain. The small black granules in the liver-cells are brownish-red anisotropic fat-droplets (cholesterol-esters), the larger black droplets irregularly scattered are deep red isotropic fat-globules (glycerol-esters). The intraperipheral zone of necrosis and beginning proliferation is well shown.

Scharlach R.—Similar results are obtained in frozen sections stained with an acetone solution of Scharlach R and counterstained with hemalum. The fine granules stain a deep red that has a distinct brownish cast, but their staining is not so intense as that of the large droplets which stain deep bright scarlet red without the brownish cast. The differential staining is about equal in the case of Sudan III and Scharlach R. I have noticed that students vary greatly in their ability to distinguish these differences with these two stains, some seeing it much better in the case of one, others with the other stain. Such results are probably ascribed to differences in color-perception due to individual training or experience in colors. With the Sudan III staining of frozen sections there seems to be at least ten times as much fat in the sections as in the case of osmic acid staining. With Scharlach R the amount of fat seems still greater, but this is probably due to the greater intensity of color in the Scharlach R stain.

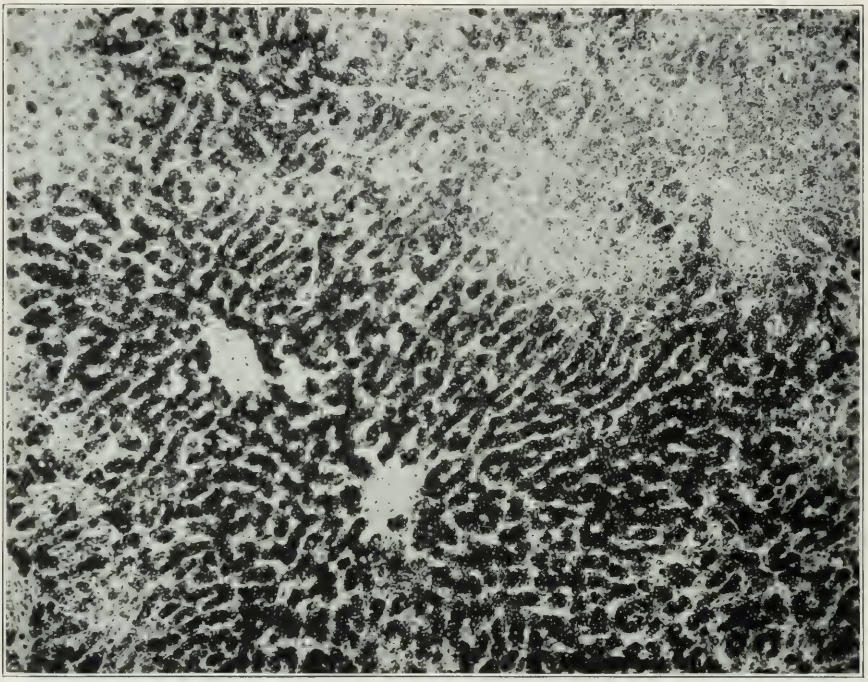

Fig. 4.—Tangential section of liver-lobules from liver of Case II. Frozen section, Scharlach R and hemalum stain. Same appearances as in Fig. 3.

Nile-blue Sulphate.—With Nile-blue sulphate the fresh frozen sections showed a great variety of color reactions with the fat droplets. The majority of the larger droplets stained red, some pink, some pink-violet, some purple, others deep blue. The majority of the fine droplets stained pink or lavender. The fine droplets in the adrenal cortex and in the lipoid cells elsewhere stain pink or lavender to violet or blue.

Weigert's Hematoxylin.—Deep blue to blue-gray droplets are shown in the larger fat cells. When counterstained with van Gieson's the blue droplets appear as darker brown droplets in the ochre-colored protoplasm.

Indophenol.—In sections stained with a saturated solution of indophenol in 70 per cent alcohol and contrasted with lithiumcarmin good fat preparations were obtained without any differential staining.

Benda's Method.—This gave no differential staining. Stains for fatty acids and soaps negative. Other staining methods (Smith-Dietrich's, etc.) were negative as far as differential staining was concerned.

Optical Appearances.—With polarized light doubly refractile (anisotropic) droplets were numerous in all the cells containing fine fat droplets. The larger cell droplets or crystals were chiefly isotropic, but anisotropic droplets were present in all cells containing fat. Crystal-like bodies appeared in the droplets on freezing. Warming caused the doubly refractile droplets to disappear. Alcohol, ether, xylol and hot paraffin dissolved all of the droplets from the cells leaving vacuoles. Acids and alkalies did not dissolve them. Chromate fixation caused the larger cell droplets to become brown or greenish. No effect was noted upon the finer ones. Formol fixation had a marked effect upon the largest fat droplets in the panniculi, causing a formation of yellowish or green needle-shaped crystals in the cell. Portions of the two livers have been kept in formol and given each year to laboratory classes for fat study. While the differential reactions shown by Scharlach R, Sudan III and osmic acid are still obtainable they are not as sharp as at first; and the Nile-blue sulphate reactions have become very capricious. At present many droplets stain blue or purplish blue. Long-continued residence in formol undoubtedly affects the fats of the

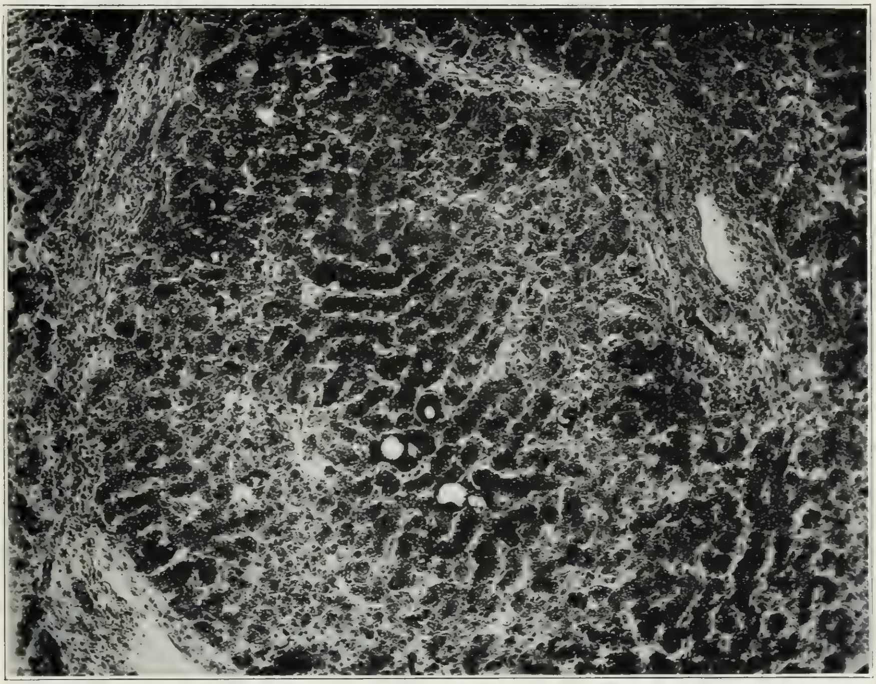

Fig. 5.—Section of liver-lobule from liver of Case I. Frozen section, Scharlach R and hemalum. Slightly higher magnification. Shows same character of lipin changes as in preceding figures, but in addition a more marked degree of peripheral necrosis and proliferation (more advanced cirrhosis).

cells. The most accurate conclusions therefore would be those drawn from the study of perfectly fresh tissues.

From the fat-reactions shown above it is evident that the livers of these two cases of hypopituitarism present an unusual lipin content. The presence of numerous anisotropic droplets, staining a lighter gray with osmic acid, brownish or yellowish red with Sudan III and Scharlach R, and pale pink with Nile-blue sulphate make it very probable that these are cholesterol-esters. Other lipoids may be mixed with these and with the glycerin-esters in these droplets. The lipin combination may be very complex. It is quite evident that our microchemical tests at the present time are not sufficiently reliable to differentiate accurately the different lipoids. We were unable to make satisfactory chemical studies of these lipins because of the fact that the greater part of the material was distributed through various fixing fluids at the time of the autopsy. The reactions are sufficiently characteristic, however, to enable us to state that the fatty changes in these cases are not those of ordinary fatty infiltration and degeneration but represent a mixed glycerin-ester and cholesterol-ester lipoidosis. Whether lecithin is present or not it is impossible to say. It is also evident that many of the liver cells contain chiefly cholesterol-esters. Further, this cholesterol lipoidosis is not confined to the liver, but occurs to a marked degree in the adrenals, in the panniculi, and to a lesser degree in scattered cells or groups of cells in other organs and tissues (spleen, aorta, kidney, etc.). In the panniculi the bulk of the lipins are probably glycerin-esters. The condition is then one of abnormal lipin metabolism

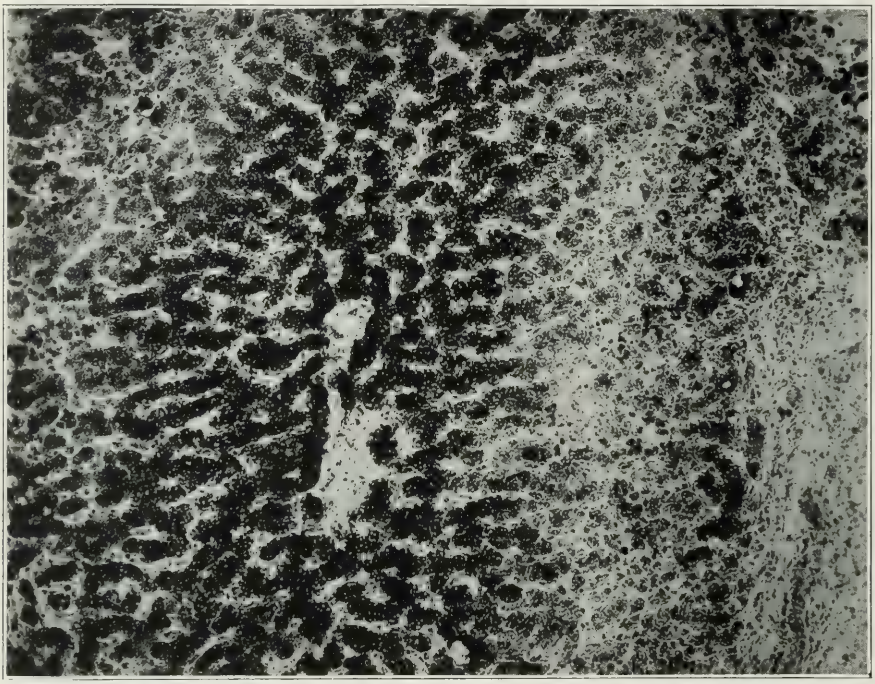

Fig. 6.—Section of liver-lobule from liver of Case II. Frozen section, Scharlach R and hemalum. Slightly higher magnification. Shows the same lipin changes, and the marked peripheral necrosis and beginning cirrhosis.

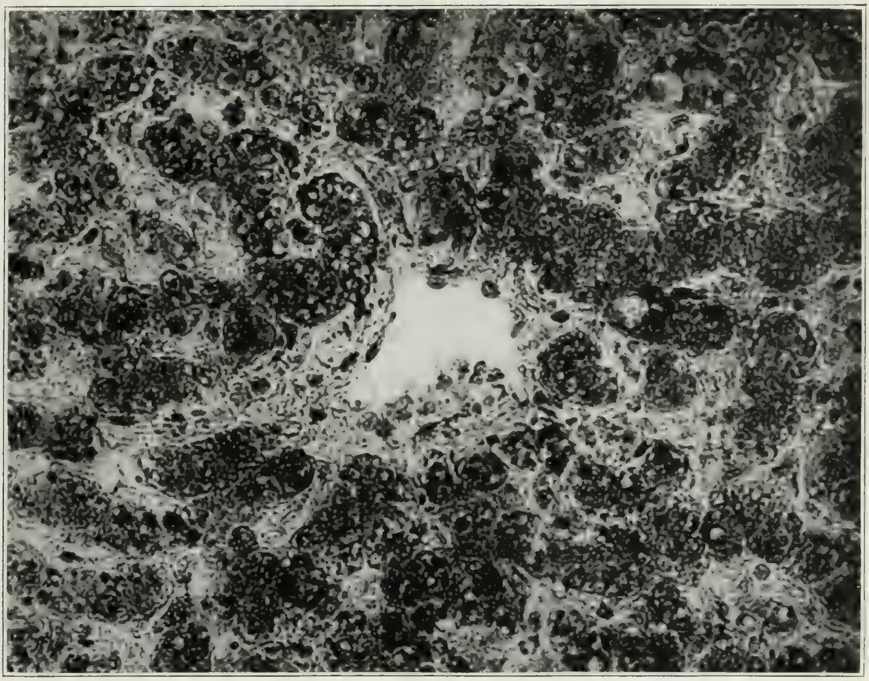

Fig. 7.—Central zone of liver-lobule from Case I. Frozen section, Scharlach R and hemalum. High power. Cells packed with small anisotropic brownish-red droplets and occasional larger isotropic deep-red globules. Cholesterol- and glycerol-ester steatosis.

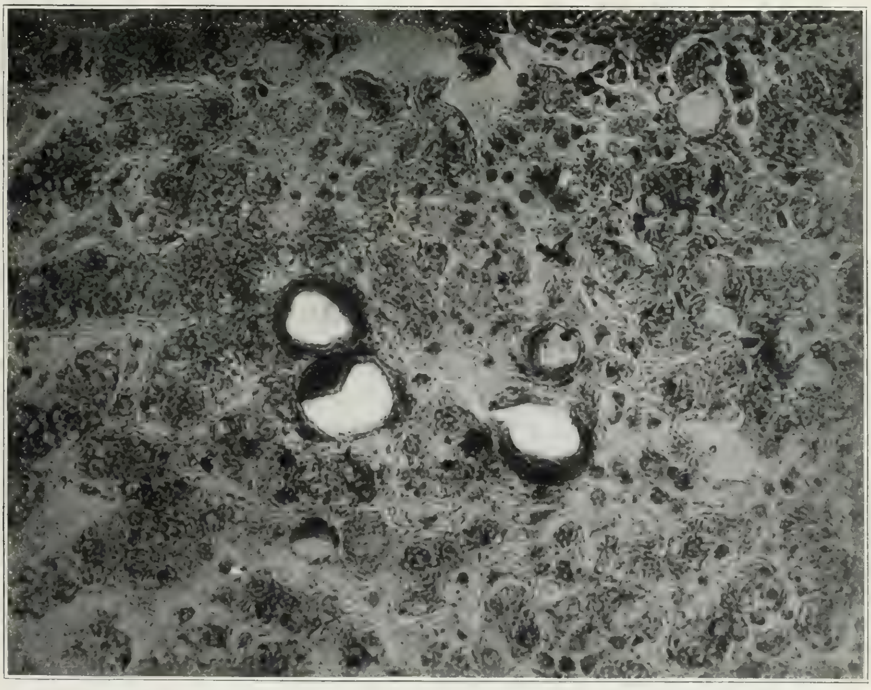

Fig. 8.—Border between mid-zone and peripheral zone of liver-lobule from liver of Case I. Frozen section, Scharlach R and hemalum. High power. To the right the zone of beginning necrosis; to the left the liver cells are filled with minute anisotropic droplets. The larger drops in the center of field with fat partly torn out in freezing are isotropic fat-globules staining deep red.

characterized particularly by cholesterin infiltration or retention (cholesterol steatosis). It is to be compared then to the cholesterol infiltrations obtained by the overfeeding with cholesterol, to the lipoidosis of diabetic lipoidemia and that of Gaucher's disease. It is, however, quite distinct in its histological picture from these conditions, although the differences as far as the deposit of the lipoids are concerned may be more of degree than of kind.

Just what relation the peculiar zonal necroses in the liver bear to the lipin metabolism, it is impossible to say. The peculiar position of this zone, intraperipheral, makes this change a unique feature in the pathology of hypopituitarism. The cause of death of the liver cells is not evident, there are no thromboses of the liver capillaries at this point, no congestion, no cause of local asphyxia, etc. That the necrosis is not altogether recent is shown by the fibroblastic proliferation and the cellular infiltration. It is, in fact, an early cirrhosis beginning, not at the periphery of the lobule, but a little distance within it, leaving outside of it a narrow zone of unaffected liver cells. In the necrotic zone all stages of atrophy and necrosis of the liver-cells can be seen. At the borders the cytoplasm of the liver cell is filled with fat-granules; these change to brownish granules, which, in turn, as the cells become smaller, become less and less visible, until only pale colorless cell bodies remain. The best explanation of this peculiar zonal necrosis is on the assumption of some toxic substance brought in the blood stream and acting upon the liver cells at this point; or else, as a result of metabolic disturbances confined to this zone of cells.

I have searched in vain through the literature for observations of a similar intraperipheral zonal necrosis, but have found nothing comparable to this form. The mid-zonal necroses associated with marked fatty infiltration of the central zone with hyperemia and necrosis of the intermediate zone are not like this; nor does it resemble the mid-zonal necrosis seen in yellow fever. There is no hyperemia, the capillaries toward the central vein are not obstructed, and the cells of the central zone, while filled with fat droplets, are not larger than normal liver cells. Finally, the necrosis is more peripheral than mid-zonal, involving the inner portion of the peripheral zone.

Both cases showed a very striking postmortem increase in temperature. Thermometer readings were taken of the second case. Seven hours after death, with all of the internal organs removed, lying on a metal table over which cold water was running, the panniculus in the flaps of the abdominal wall still were unpleasantly warm to the touch, and showed a temperature or 104°. A large slice of the abdominal wall showed the same temperature some time after removal from the body. A clinical thermometer plunged into the liver gave a reading of 108°. It is most probable that this excessive heat-production is related to the abnormal fat deposits, and to postmortem changes in the lipins of the cell.

SUMMARY.

In hypopituitarism there is a peculiar obesity due to infiltration of various cells of the body with a mixture of lipins:—glycerin-esters and cholesterol-esters. This condition of cholesterol liposis is especially marked in the liver and adrenals, but is scattered all over the body. With deficiency of hypophysis function there appears to be associated a cholesterol retention or infiltration. Hypopituitarism must, therefore, be classed among the xanthelasmic conditions, and is related in kind to diabetic liposis and Gaucher's disease.

The hypophysis is either directly or indirectly concerned with lipin metabolism, particularly with cholesterol steatosis. Postmortem hyperpyrexia may be associated with hypopituitarism and the obesity resulting from the latter condition.

In the livers of two cases of hypopituitarism there occurred a peculiar intraperipheral zonal necrosis, unlike all previously described forms of zonal liver necrosis. Associated with this necrosis is a reparative fibroblastic proliferation, giving rise to the picture of an early intralobular cirrhosis. The relationship of this hepatic change to the hypophysis conditions remains to be shown.

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SYPHILIS OF THE PULMONARY ARTERY: SYPHILITIC ANEURYSM OF LEFT UPPER DIVISION: DEMONSTRATION OF SPIROCHETE PALLIDA IN WALL OF ARTERY AND ANEURYSMAL SAC*

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SYPHILIS of the pulmonary artery is considered one of the great rarities. There is but little literature concerning it. The ordinary textbook does not mention it. The few cases reported in which lesions of the pulmonary artery wall were regarded as syphilitic, rest entirely upon the character of the histologic changes. *Spirochete pallida* has not, up to the present time, been demonstrated in these lesions. It follows, therefore, that only those lesions of the pulmonary artery definitely *gummatous* in character can have been regarded as syphilitic with any degree of certainty. This criterion narrows greatly the number of observations in which the changes in the pulmonary artery can be accepted as in all probability syphilitic. We may conclude from this that gummatous changes, at least, are of very rare occurrence in the pulmonary artery.

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Nevertheless, sclerotic and atherosclerotic changes in the pulmonary artery have been so much more frequently mentioned in the literature that we must believe that lesions of this type must be of far greater frequency than gummatous lesions. The part that syphilis plays in the etiology of these sclerotic processes has, however, been very difficult of determination; and very few authors have ascribed to syphilis any important role in their production. By the great majority of observers the atherosclerosis of the pulmonary artery of the moderate degree so often seen at the autopsy table has been regarded as but an incident in the picture of a general atherosclerosis, or as resulting from long continued increase of blood pressure in the pulmonary vessels in such conditions as mitral stenosis, emphysema, etc. In these cases the pulmonary atherosclerosis is without clinical significane. In but a small number of cases (Mönckeberg, Romberg, Aust, Rogers, Sanders, Barlaro, etc.) has there been observed an extensive pulmonary atherosclerosis apparently of primary clinical importance (symptoms of chronic cyanosis, etc.). The writer has under study the autopsy material of such a case of pulmonary atherosclerosis presenting clinically the picture of polycythemia. These cases probably fall into the class styled "Ayerza's disease" by Barlaro.

Macroscopically these most common forms of pulmonary atherosclerosis consist usually of yellowish or yellowish-white, more rarely porcelain-like, thickenings of the arterial wall, chiefly of the intima. These thickenings are usually elevated, and may be plaque-like or nodular, or more diffuse. Calcification is rare; and atheromatous ulcers appear not to have been observed. (In my case of chronic polycythemia there were extensive atheromatous ulcers in the pulmonary arteries.) Microscopically the lesions have been described as similar to those of general atherosclerosis, consisting essentially of a thickening of the intima with hyaline change of the fibrous tissue and secondary atheromatous degeneration. The relation of syphilis to these changes in the pulmonary artery has been as much disputed relatively as it has been in the case of systemic atherosclerosis. At the present time the majority of writers regard them as nonsyphilitic in origin.

As to the occurrence in the pulmonary artery of the form of mesarteritis that very recently has come to be pretty generally regarded as syphilitic in etiology (since it occurs in the aorta of all known syphilitics coming to autopsy, and has been shown to be associated with spirochete localization) but little is known. In the aorta this type of vessel lesion is characterized macroscopically by thickening, or often thinning, of the vessel wall, with loss of elasticity, hyaline change without much tendency to calcification or atheromatous change, and linear or radiating contractures or fissures of the intima. Microscopically the essential syphilitic characters of this process are the lymphocyte and plasma-cell infiltrations along the vasa vasorum of the adventitia and media, obliteration of these vessels, atrophy, fibrosis, hyaline change and secondary atheromatous changes in intima and media. In my experience mesaortitis of this type is always syphilitic. I believe, however, that healed syphilitic mesaortitis can not be distinguished microscopically from ordinary atherosclerosis; and, on the other hand, the macroscopic appearances of ordinary atherosclerosis may yield the microscopic picture of an active syphilitic process. I also believe that the terms "mesaortitis" and "mesarteritis" are misapplied. All coats of the vessel are involved; and the most active process is usually found in the adventitia. It is essentially a disease involving the vasa vasorum; and the changes in the intima and media are secondary to the disturbance of circulation in the small nutrient vessels of the artery. They consist of a slow atrophy, fibrosis, secondary hyaline change and atheromatous degeneration; and are perhaps to be interpreted as of the nature of a slow infarction. The essential diagnostic features of this form of syphilitic disease of the vessels are the active infiltrations about the vasa vasorum. The macroscopic picture may be characteristic (as described above) in some cases, but in many the gross changes may be wholly those of ordinary atherosclerosis. The microscopic appearances alone can decide the question; and this only when the process is still active. In these active perivascular (vasa vasorum) infiltrations the spirochete may be found in properly-prepared Levaditi blocks made from cadavers still warm.

The occurrence of this form of syphilitic arteritis leading ultimately to atherosclerosis has been noted almost wholly in the aorta; and the other large arteries of the body have not been given much attention with respect to their involvement in the process. As far as the pulmonary artery is concerned there exist a very few observations in which this type of arteritis was found affecting this vessel. These observations will be listed below.

The subject of aneurysm of the pulmonary artery also receives very scant attention in the textbooks and general literature. It is not mentioned at all by the majority of writers. Benda, *Aschoff's Specielle Pathologie, Zweite Auflage*, 83, says that of the visceral arteries the cerebral, pulmonary and splenic arteries are most frequently the seat of aneurysms. He undoubtedly refers to the small aneurysms of the size of a pea or bean found in tuberculous cavities, and from which fatal hemorrhage frequently takes place. These are mentioned also in the articles on pulmonary tuberculosis. The writer has been unable to find in any textbook any mention of syphilitic aneurysm of the pulmonary artery. Of the reviews of the general literature on the subject of pulmonary aneurysm the monographs of Henschen (1906) and Posselt (1909) are the most important and complete.

SURVEY OF LITERATURE

The literature of syphilitic disease of the pulmonary artery has been reviewed by Posselt up to the year 1909. He calls attention to the fact that although a luetic basis for arteriosclerosis of the pulmonary artery was early suspected the majority of the cases reported rested upon very vague surmises. In others the syphilitic nature of the changes in the pulmonary artery was assumed because of a history of syphilis in the patient, or because luetic processes were found in other organs. The majority of the reported cases were observed before the discovery of the spirochete and the Wassermann reaction; and in a large number the pathologic description is too poor or too incomplete to permit definite conclusions as to the nature of the process.

Neumann, in his article on syphilis in the *Nothnagel System*, 1896, says: "An idiopathic syphilitic diffuse inflammation of the pulmonary artery has to my knowledge not yet been observed."

Posselt says that so far as he can see the arteriosclerotic processes in the pulmonary artery lack the specific characteristics that are present in endaortitis luetica, although in a few cases the descriptions come close to it. He further says that luetic processes in the pulmonary artery must be extraordinarily rare since the great textbooks and handbooks of internal medicine, pathologic anatomy, and syphilis give no attention to it.

Rach and Wiesner state that in children having congenital lues who die within the first weeks of life, disease of the great vessels (aorta and pulmonary artery) is one of the relatively frequent findings; but they were unable to demonstrate the presence of spirochetes in these lesions. The writer has seen such lesions in the intima of the aorta and in the endocardium of cases of congenital syphilis in which spirochetes were found in large numbers. These lesions, however, were very different from the arterial changes in adult syphilis; they were primarily colonizations of the spirochetes in the intima resulting in a fibroblastic proliferation of the latter.

Rejecting all but the most probable cases, the reported observations upon the occurrence of syphilis of the pulmonary artery may be classed as follows:

1. *Gumma of the Pulmonary Artery*

1. *Weber, 1863.*—Girl, 21 years of age, had been treated for secondary syphilis. Autopsy showed gummata of skull, liver and right pulmonary artery.

2. *Wagner, 1866.*—Male, 31 years old, history of syphilis for eight years, showed at autopsy gummata of myocardium, tongue, pectoralis major muscle, pericardium, skull and pulmonary artery.

3. *Sequiera, 1897.*—Male, aged 37 years, died suddenly, showed at autopsy a tumor in the wall of the pulmonary artery just above the semilunar valves. From its microscopic structure it was regarded as a gumma.

4. *Hanford, 1904.*—Woman, aged 32, with history of dyspnea and fainting attacks, showed at autopsy gummata of the interventricular septum and the wall of the pulmonary artery just above the valves.

2. *Gummatous Arteritis of the Pulmonary Artery*

1. *Schwalbe, 1890.*—Woman, 53 years old, had symptoms of palpitation, dyspnea edema and cyanosis for six weeks. Autopsy showed sclerotic changes and multiple small gummata in the pulmonary artery.

2. *Kasem-Beck, 1900.*—Male, aged 50 years, with symptoms of decompensation, showed at autopsy sclerotic changes in the pulmonary artery associated with multiple small gummata.

He refers to a case reported by him in 1889, showing also a gummatous arteritis of the pulmonary artery.

3. *Wagner and Quiatkowski, 1903.*—Male, aged 49 years, with history of untreated syphilis, symptoms of dyspnea, palpitation and general edema. Autopsy showed gummata of the heart, healed gumma in liver, and a gummatous arteritis of the pulmonary artery.

4. *Winternitz and Schmeisser, 1917.*—Two cases reported at the meeting of the International Association of Medical Museums, April, 1917, New York. Through the kindness of Dr. Winternitz I am permitted to make note of these cases, a study of which will soon be published.

Case 1. Male, colored, aged 27 years, had chancre and skin rashes at age of 17. Positive Wassermann. Admitted with symptoms of multiple aneurysms. Autopsy showed syphilitic arteritis of aorta, pulmonary, splenic and right femoral arteries; saccular aneurysms of the arch, descending aorta, splenic and right femoral arteries; fibrous orchitis; syphilitic cirrhosis of the liver; healed gumma (?) of kidney; pseudolobar pneumonia with abscess; fibrinopurulent pleurisy.

Microscopic examination of the pulmonary artery showed a syphilitic arteritis with gummatous areas.

Case 11. Male, colored, aged 56 years, without history of venereal disease, was admitted to Dr. Barker's service in the Johns Hopkins Hospital complaining of "shortness of breath." Two Wassermanns were negative. Autopsy showed fibroid induration of lungs; chronic adhesive pleuritis; mesarteritis of pulmonary artery with aneurysm of right main branch; thrombosis of sac; hypertrophy and dilatation of right ventricle; miliary gummata or tubercles of liver; chronic passive congestion; ascites; edema.

Microscopic examination of the wall of the pulmonary artery gave a typical picture of syphilitic mesarteritis with gummatous nodules.

Spirochetes were not demonstrated in either case.

3. *Nongummatous Arteritis of the Pulmonary Artery*

In this group can be placed only those cases in which there was a definite probability that the changes in the pulmonary artery were due to syphilis. In the absence of gummatous lesions the observers recording such cases could only assume their syphilitic nature either because of a definite clinical history of that disease or because the pulmonary lesions were associated with well-marked lesions of syphilis in other organs. The presence of the spirochete pallida in these lesions has not yet been demonstrated in any case. In an analysis of 172 cases of pulmonary arteriosclerosis gathered from the literature Posselt found syphilis to be the most important associated condition in 6.9 per cent. It is interesting to note, however, that myocarditis was the associated finding in 15 per cent of cases, and arteriosclerosis in 12.6 per cent. The importance of syphilis as an etiologic factor in these two conditions enhances its probable relationship to pulmonary sclerosis.

Brüning (1901) thought that it was not improbable that syphilis was of some importance in the etiology of pulmonary sclerosis.

Thorel (1903) stated that the etiology of pulmonary sclerosis remained unsolved if syphilis were not considered.

Henschen (1906) came by exclusion to the hypothesis that narrowing and sclerosis of the pulmonary artery in the majority of cases were due to syphilis.

Rogers (1909) states that in Bengal pulmonary arteriosclerosis is not a rare cause of fatal dropsy, and believes that when it occurs between the 20th and 40th years it is apparently caused by syphilis.

Reported Cases of Syphilitic Pulmonary Arteriosclerosis

1. *Dickinson, 1862.*—Male, aged 40, with fibroid myocarditis and pulmonary sclerosis.

2. *Payne, 1874.*—Woman, aged 33 years. Sclerosis of pulmonary artery and branches without known cause. Lues (?).

3. *Wallis, 1887.*—Girl, aged 23. Father luetic. Marked hypertrophy of heart with normal valves. Sclerosis of aorta and pulmonary artery. Lues (?).

4. *Friedrich, 1889.*—Case showed gummatous nodules in wall of aorta. Induration of the wall of the pulmonary artery and narrowing its lumen.

5. *Grigorjew, (Cited by Posselt).*—Woman, aged 34, with syphilis and pulmonary aneurysm.

6. *Loveland, (Cited by Henschen).*—Man, aged 51 years, with syphilis and pulmonary aneurysm.

7. *Brüning, 1901.*—Two cases of pulmonary sclerosis associated with syphilis. Male, aged 54, with lues, aortic and pulmonary sclerosis. Male, aged 72, luetic changes in various organs. Sclerotic changes in pulmonary artery.

8. *Wagner and Quiatkowski, 1902.*—Male, aged 49 years, with syphilis, luetic endarteritis of the pulmonary artery, and pulmonary aneurysm.

9. *McPhedran and Mackenzie, 1903.*—Male, aged 55 years, miliary gummata in liver, sclerosis of pulmonary artery, thrombosis, and infarction of right lung.

10. *Ribbert, 1905.*—Case of fatal syphilitic obturation of right branch of pulmonary artery, gummatous aortitis.

11. *Westenhoeffer, 1906.*—Woman, aged 34 years, with extensive syphilis of the arterial system, including the pulmonary artery.

12. *Henschen, 1906.*—Woman 42 years old. No history of syphilis. Myocardial insufficiency and aneurysm of pulmonary artery. Microscopic picture of syphilitic arteritis.

13. *Brooks, 1907.*—Woman, aged 34, who had had one miscarriage, but no other history of syphilis, showed right-sided hypertrophy of heart and extensive sclerosis of pulmonary artery. Syphilis regarded as the most probable cause.

14. *Rogers, 1909.*—Hindu, male, aged 38 years. History and scars of syphilis. Right-sided hypertrophy of heart. Marked sclerosis of pulmonary artery.

15. *Barth, 1910.*—Male, aged 57 years, no history of syphilis. Six years before had slight "stroke." Autopsy showed old pachymeningitis, right-side hypertrophy of the heart, aneurysm of pulmonary artery, and fibrous orchitis. Microscopically, the pulmonary showed changes precisely like those of syphilitic aortitis.

4. *Syphilitic Aneurysm of the Pulmonary Artery*

The literature of aneurysm of the pulmonary artery up to 1909 has been reviewed by Posselt. Henschen, in 1906, had thoroughly sifted and criticized the literature, collecting 42 cases; and Posselt increased this list by nine cases. As mentioned above Henschen, by exclusion came to the conclusion that syphilis must be the most probable etiologic factor in the production of pulmonary sclerosis and aneurysm. Of Henschen's cases of pulmonary aneurysm with arteriosclerosis all with one exception were between the ages of 24 and 42. He regards this as a strong point in favor of syphilis. Of the nine cases added by Posselt six were between 20 and 40 years, and the ages of the other three were 45, 54, and 71 years. Posselt agrees with some reserve to Henschen's opinion, and points out the necessity of applying the Wassermann reaction and spirochete demonstration to the solving of the question.

CASE HISTORY

History of Case.—(Medical Clinic of University Hospital: Dr. Foster). Mr. R. McG., aged 37 years, American, machinist.

Family history good.

Patient had measles, mumps and whooping cough during childhood; smallpox in 1907. Has had two gonorrheal infections. Had hard chancre in 1899; for this he received only local treatment. Does not smoke; drinks but little; has generally had very good health.

Patient entered the hospital because of hemorrhage from the lungs. About September, 1916, in the evening he suddenly expectorated about half a pint of blood without any apparent cause. Felt no bad effects. Two weeks after had another hemorrhage of about a quart. This happened at the end of a day's work. He quit work for seven weeks, and during this time he had hemorrhages of 1 to 2 pounds in amount about every four days, even when resting in bed. After returning to work he had hemorrhages also. On December 16, 1916, while working he lost over two quarts. Since then he has done no work. Has had three hemorrhages since January 2, 1917. Has gained in weight during the last four months. Has had no night sweats. Has some hoarseness and cough. Every 2 to 3 hours he brings up some blood-tinged mucus. During the hemorrhages he has some pain through thorax. He has no symptoms of tuberculosis or aneurysm. Sleeps well. Bowels regular.

Physical examination on entrance showed a man of large frame, good nutrition, weight 174 pounds. Musculature is good; panniculus scanty. Temperature 98°. Pulse 90. Respirations 22. Skin smooth, warm, moist, showing few pits from smallpox. Pupils regular, equal, react to light. Accommodation normal. Sclera is clear. Mucous membranes are pale. Tongue protrudes straight, no tremor. Teeth in poor condition. Throat negative. No palpable cervical glands. Diastolic pulsation in neck. Thyroid negative.

Thorax.—Inspection negative. No lagging. Percussion negative. Vesicular breath sounds; a few scattered rales on the right lower front. Slight increase in whispered voice over left third and fourth interspaces. Palpation, percussion and auscultation of back negative.

Heart.—Apex in 5 i. c. s., half inch outside nipple line; marked diastolic sound in 3 i. c. s., transmitted upwards and across.

Abdomen.—Wide epigastric angle. No tenderness. Liver and spleen not palpable.

Radial pulse regular and equal; tension normal. Systolic pressure 130, diastolic 88. Stools and urine negative. Red blood cells 3,950,000; whites 7,300. Slight increase of lymphocytes. One normoblast. Hemoglobin 43.

Reflexes active and somewhat exaggerated on both sides.

No edema. No adenopathy.

Wassermann + + + +

Provisional Diagnosis.—Tuberculosis (?); syphilis of the lung (?); weeping aneurysm (?).

Feb. 2, 1917.—Diagnosis of syphilis of the lung made, and patient referred to clinic of syphilology for treatment. (Dr. Wile). He had no hemorrhage while in the medical clinic, but shortly after being transferred he lost over a pint of blood. At this time the right radial pulse was noted to be larger and stronger than the left. Patient appeared more anemic. Visible cardiac pulsation five inches to left of midsternal line.

In the clinic of syphilology he received a single intravenous dose of 4 mg. neosalvarsan and daily inunctions of blue ointment. He also received a transfusion of about 300 c.c. of citrated blood following a hemorrhage.

Feb. 14, 1917.—Report from department of roentgenology (Dr. Van Zwaluwenburg). "These are very unusual plates. The diaphragm is high, and the density of the lung shadow is apparently great. The left side, however, is denser than the right below the second rib. This opacity is more or less diffuse, especially on the costal margin; and in particular, there is a mass—a shadow—in the left postscapular line, extending from the second to the fourth rib, slightly larger than a hen's egg, fairly sharply defined on its outer border, but poorly defined elsewhere. It seems separated by a small space from another similar shadow occupying the right upper hilus. This chest is so wide that the pleural border is not well shown.

These shadows do not have the characteristics of tuberculosis or of ordinary inflammatory infiltrations. The exact underlying pathology is not discovered. This is suggestive of neoplasm."

Feb. 16, 1917.—Physical examination at this time shows marked

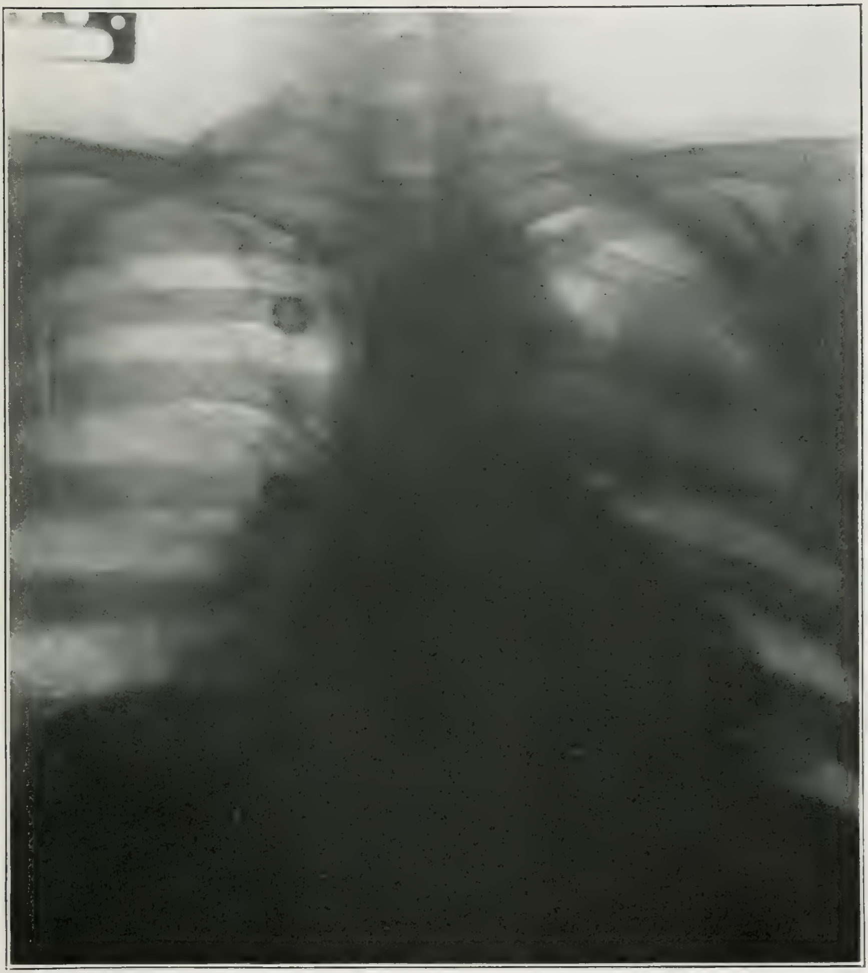

Fig. 1.—Roentgen ray plate chest. Shadow of aneurysm shows as a mass, somewhat larger than a hen's egg, on the left extending from second to fourth ribs, fairly well defined on its outer border, but less well defined elsewhere. The density of the lung shadow on both sides is great, but more marked on left below the level of the second rib.

pallor and weakness. Patient is nauseated and vomits after almost every meal. He is markedly dyspneic. There is well-marked edema of the ankles. At the cardiac apex there can be heard a loud rough to and fro murmur, definitely influenced by pressure with the stethoscope, and transmitted all over the left chest and into the axilla. The urine contains about 8 grains albumin per liter, and many granular and cellular casts.

Patient was unable to take much by mouth and was given water by rectum, containing five grains sodium bicarbonate, two grains sodium citrate and one grain potassium iodide to the liter. This was well retained; but towards evening the dyspnea became more marked, the extremities were cold and covered with cold sweat; and the patient complained of dull pain all over the thorax and abdomen. Death occurred at 11:00 P. M.

Clinical Diagnosis.—Lues. Gumma of Lung. Anemia.

Autopsy by Dr. Warthin, at 8:00 A. M., 2-17-17. The autopsy protocol is as follows:

AUTOPSY PROTOCOL

General Inspection.—Length 175 cm. Strong athletic build. Bones large. Thorax large; epigastric angle 180°. Left side more prominent than right, particularly in cardiac area. Musculature well developed; muscles firm. Rigor mortis present throughout. Panniculus is moderate. General edema. Skin pale, discolored over the sternum. Superficial vessels contain little blood. Hypostasis very pale. Mucous membranes very pale. Lips and tongue covered with grayish coating. Teeth poor. Foul odor from mouth. Facies older than of his age. Beard slightly gray.

Head and *spinal cord* were not examined.

Main Incision.—Panniculus on section is pale and moist. No gas in the peritoneal cavity. Small amount of clear, amber fluid. Omentum fatty, anemic. Position of abdominal organs normal. Peritoneum clear, moist, shining. Diaphragm on the right at lower border 4th rib; on left at upper border of 7th rib. Costal cartilages cut easily with exception of first on both sides. Sternum rather sclerotic, marrow not hyperplastic. About 300 cm. clear fluid in left pleural cavity; small amount in right cavity. Mediastinal fat abundant, pale, containing pigmented lymph nodes. Thymic fat abundant. Apex behind 7th rib, outside the anterior axillary line.

Heart.—Bovine heart, 17x16.5x8 cm. (after opening). Pericardial adhesions on both sides. Intrapericardial tension increased. Fluid increased in amount, cloudy. Pericardial surfaces cloudy, covered with creamy layer of fibrin. Vessels injected. Epicardial sclerosis over anterior wall of right ventricle. Venæ cavæ greatly dilated. All cardiac chambers greatly dilated. Large agonal white clots in venæ cavæ and auricles. Heart weighs 700 grams after removal of clots and blood. Left ventricle dilated; wall hypertrophic, showing diffuse fibroid patches. Endocardium thickened. Papillary muscles hypertrophic, show marked fatty change ("tiger heart"). Wall 17 mm. thick. Right ventricular wall is 7 mm. in thickness, about one-half being fat tissue. Cavity of right ventricle and auricle greatly dilated. Mitral orifice is relatively insufficient; large agonal clots are attached to its flaps, the edges of which show marked sclerosis. Hydrostatic test of aortic valves shows insufficiency. Valve flaps show slight sclerosis; insufficiency is relative. Tricuspid opening admits entire hand, relative insufficiency. Agonal mixed and chicken-fat clots attached to flaps. Pulmonary orifice admits three fingers. Mixed and lardaceous agonal clots in pulmonary artery. Pulmonary artery much dilated and shows marked sclerosis.

Aorta.—The ascending portion of the arch is dilated, and shows marked syphilitic aortitis. Linear and irregular fissures with hyaline change, atheroma, and porcelain-blue thinnings of the wall are seen throughout the entire length of the aorta. In the ascending portion there are two atheromatous ulcers.

Lungs.—The left lung is free except posteriorly, where there are firm adhesions over a firm mass about the size of a hen's egg, near the root. On section lung shows marked congestion and edema. Weight 858 grams. There is a well-marked induration of the lung tissue. All of the blood vessels are dilated, and greatly thickened. The pulmonary artery is greatly enlarged, as thick as a finger, and when opened shows marked atherosclerosis of its wall, hyaline areas alternating with yellowish plaques. The division to the upper lobe forms a round aneurysmal dilatation, of the size of a guinea hen's egg, nearly filled with a laminated red clot, part of which is old and part more recent. The thrombus is firmly adherent to the wall on the posterior side of the sac. The wall of the sac is directly continuous with the lumen of the artery; it presents the gross appearances of a syphilitic arteritis, in all respects resembling syphilis of the aorta. No break in the sac is present, and no macroscopic hemorrhage is

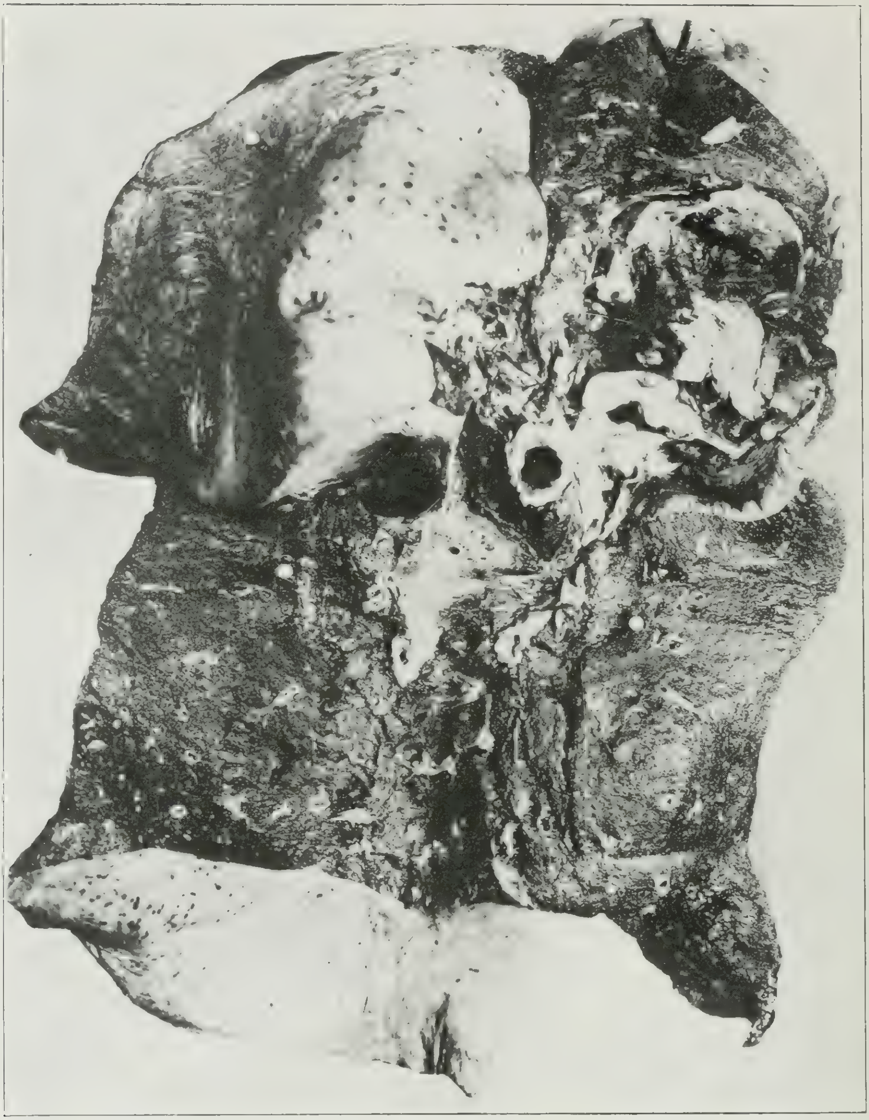

Fig. 2.—Photograph of left lung showing the opened aneurysmal sac of the main branch of pulmonary artery in upper lobe. Lying in the sac is a laminated blood clot. Just below the aneurysm, to the right of the branches, the slit-open dilated pulmonary artery shows very well the marked sclerosis of its wall. Throughout the entire lung the smaller branches of the arteries show marked sclerosis.

seen about it. The lung tissue about the aneurysm is much compressed, atelectatic, and brownish gray in color. The entire left lung presents the appearance of a very marked chronic passive congestion with sclerosis of the vessels. The right lung is free throughout. Beneath the pleura on the outer surface of the lower lobe there is a calcified healed tubercle. The lung presents the same appearances of a chronic passive congestion with sclerosis of the vessels as does the left. No pneumonic areas in either lung. Anthracosis is marked in areas. The bronchial nodes are heavily pigmented, and on the left are much enlarged, indurated and edematous. *Bronchi* are negative.

Esophagus.—Negative.

Spleen.—Lower border two finger breadths above edge of ribs. Weighs 275 grams; measures 13x9x6 cm. Plump. Stroma increased. Chronic passive congestion.

Stomach.—Marked atrophy of mucosa.

Intestines and Appendix.—Negative.

Pancreas.—Small, firm. Marked fatty atrophy. Lobules small, well outlined. Consistency firmer than normal, especially towards head.

Liver.—Weighs 2600 grams; measures 26x22x11 cm. Still warm. Lower edge smooth. On the anterior surface of right lobe there is an umbilicated depression 4x7 cm. Above this there are a number of smaller depressions. Over these the capsule is thickened. On section the liver surface shows increase of stroma and atrophy of lobules with fibroid areas corresponding to the depressions in the surface. The largest one has a caseous center stained with bile. The appearances are those of a syphilitic cirrhosis with multiple gummata, the majority of these in a healing state. *Gall bladder* and *portal vein* were negative. *Mesenteric lymph nodes* negative.

Adrenals.—Both adrenals deeply embedded in fat. Cortical portion shows excessive lipoidosis. Medullary portions show postmortem softening.

Kidneys.—The left kidney weighs 600 grams, and measures 17x11x7 cm. Enormous fatty capsule. The fibrous capsule is adherent. Cortical surface smooth; slight fetal lobulation. Few small retention cysts. Kidney very anemic; cut surface cloudy, slight brownish in color. Cortex above pyramids measures 5 to 6 mm. Outlines of labyrinths and medullary rays are not distinct.

The right kidney weighs 550 grams, and measures 16x10x6.5 cms. On section shows appearances similar to those of left kidney.

Bladder.—Negative.

Prostate.—Negative.

Seminal Vesicles.—Negative.

Penis.—Genitals large. Scrotum low-hanging. Foreskin tight; large amount of smegma. Shallow ulcerations and erosions over glans and foreskin.

Testicles.—Large and firm. On section the right testis shows some fibrosis; the left testis shows larger patches of fibrosis.

MICROSCOPIC EXAMINATION

Heart.—Fatty infiltration of subepicardial tissue. Early pericarditis. Hypertrophy and atrophy of muscle. Fatty degeneration of papillary muscles ("tiger heart"). Diffuse fibrosis. Active areas of plasma-cell infiltration, syphilitic myocarditis.

Aorta.—Advanced atherosclerosis of intima and media. Lymphocyte and plasma-cell infiltrations along vasa vasorum of adventitia and media. Obliteration of the small arterioles. Typical syphilitic aortitis ("mesaortitis"). One of the atheromatous ulcers shows a small attached thrombus and a beginning dissecting aneurysm tear in the intima.

Lungs.—Marked brown induration. Great numbers of pigmented "Herz-fehler" cells in the alveoli. Chronic passive congestion and edema. Thickening of alveolar walls, interlobular septa and vessel walls. All branches of pulmonary arteries show more or less sclerosis and are greatly dilated. In the neighborhood of the aneurysm there is marked atelectasis with old and more recent hemorrhages into the alveoli. Hypostatic congestion in both lower lobes. Calcareous tubercle in lower right. No pneumonic areas. No syphilis of lung tissue or bronchi. *Bronchial nodes* are moderately anthracosed. They present a marked new formation of blood vessels with concentric thickening of the walls and obliteration of their lumina. Plasma-cell infiltrations occur about the vessels. Syphilitic lymphadenitis.

Wall of Aneurysm.—An old red clot, somewhat laminated, rests upon the hyaline, sclerotic thickened intima of the artery. The thrombus shows but little organization. Secondary atheromatous changes occur in portions of the hyaline intima. The media is al-

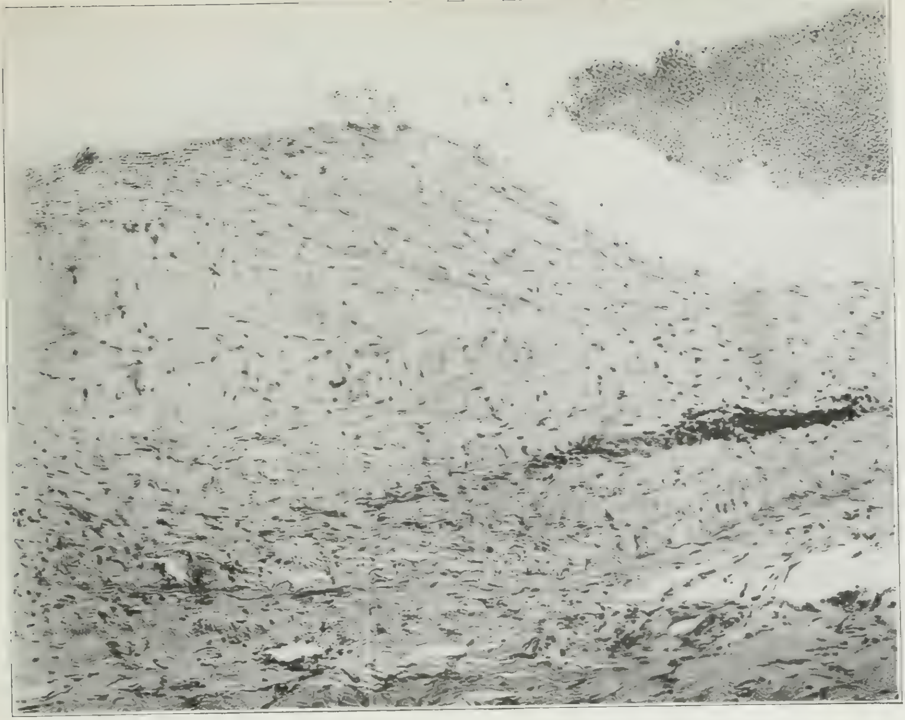

Fig. 3.—Photomicrograph of sclerotic pulmonary artery wall, intima side. Marked fibrosis of intima, with small collections of plasma cells about the small vasa vasorum. Syphilitic arteritis.

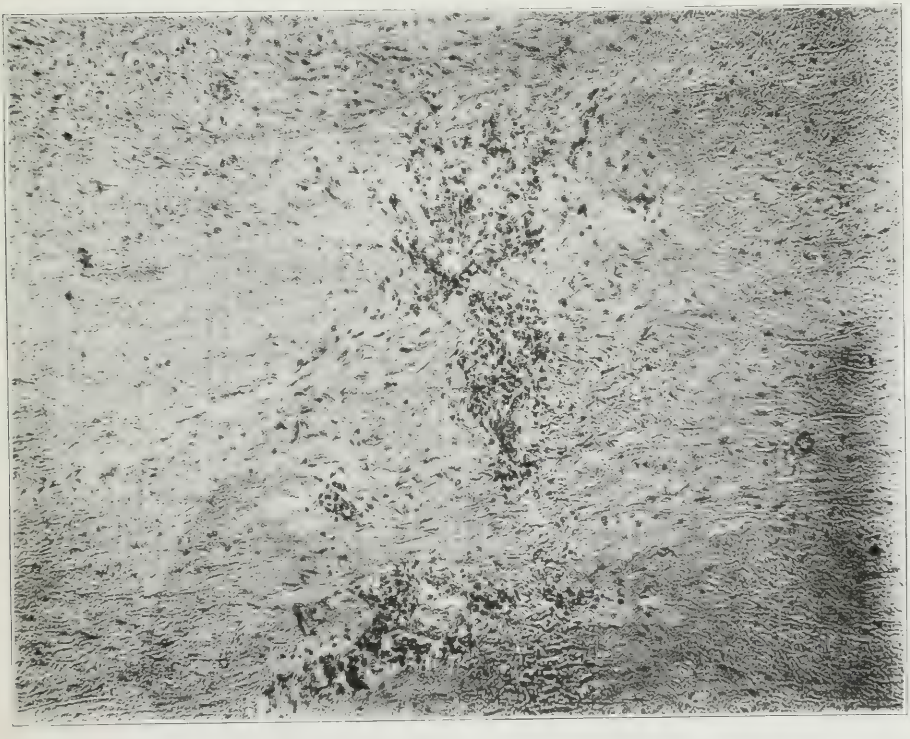

Fig. 4.—Photomicrograph of media of thickened sclerotic pulmonary artery. Typical picture of syphilitic mesoarteritis; infiltrations of lymphocytes and plasma cells along the vaso vasorum; marked fibrosis.

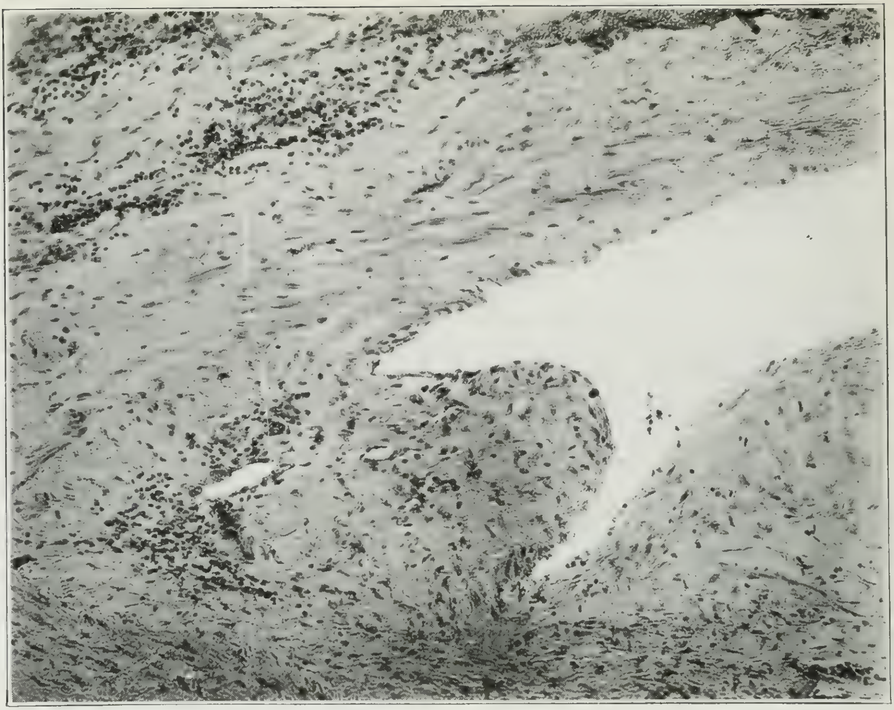

Fig. 5.—Syphilitic arteritis of pulmonary artery. Lymphocyte and plasma cell infiltrations in wall of artery at point of branching.

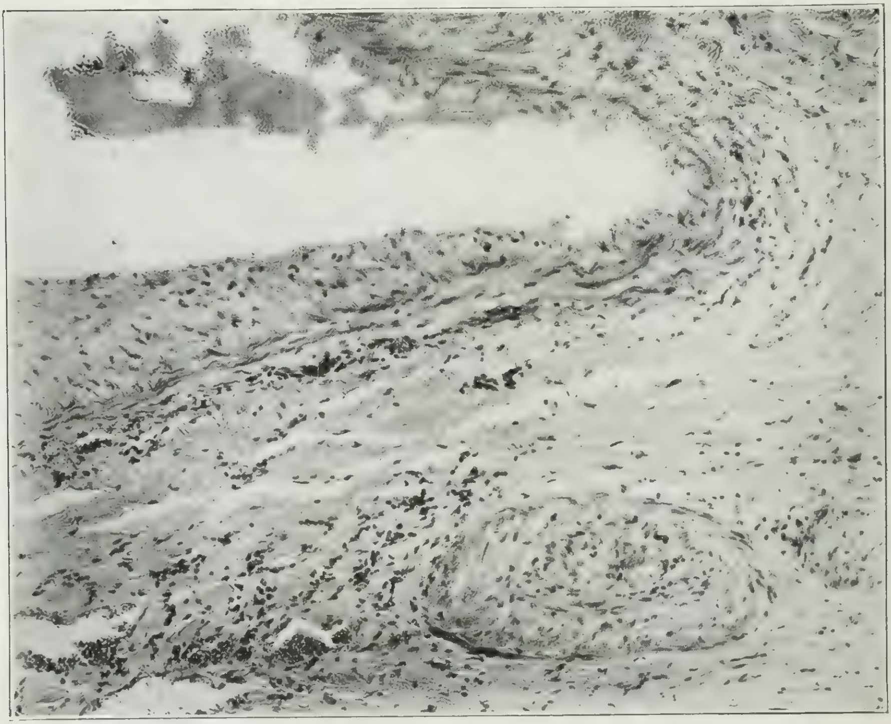

Fig. 6.—Syphilitic arteritis of pulmonary artery; small plasma cell infiltrations; fibrosis; obliteration of one of the vasa vasorum.

most entirely replaced by a dense hyaline fibrous tissue, in which only a few unstriped muscle cells can occasionally be recognized. In this connective tissue there are many new vessels; the arterioles have greatly thickened walls, and many show an active proliferating endarteritis. Around the small veins there are plasma-cell and lymphocyte infiltrations and fibroblastic proliferations, extending along these and the capillaries from the adventitia up through the media to the intima. Small infiltrations of plasma-cells occur throughout the media. The process is precisely the same as that seen in syphilis of the aorta. In the outer portion of the aneurysmal wall compressed alveoli filled with pigmented phagocytes are seen. Outside of these the alveoli are atelectatic and contain more recent hemorrhages. The small bronchi in the neighborhood contain mucus and fresh blood.

Pulmonary Artery.—Sections of the sclerotic pulmonary artery and its divisions show a syphilitic arteritis in all respects identical with the process of syphilis of the aorta. The intima is thickened, hyaline, with patches of atheromatous change; the media shows fibroid areas and infiltrations of lymphocytes and plasma-cells extending along the vasa vasorum, these increasing in the adventitia, with proliferating endarteritis of the small arterioles, obliteration of their lumina, fibroblastic proliferation and new formation of capillaries in the vessel wall.

Spleen.—Atrophy. Chronic passive congestion. Sclerosis of vessels. Increase of stroma. Hyaline change in some of the follicles.

Liver.—Diffuse syphilitic hepatitis, with multiple gummata; some in active stage, others healing. Brown atrophy and chronic passive congestion.

Pancreas.—Fatty atrophy. Patches of active syphilitic infiltrations. Acini dilated.

Intestine.—Hyperplasia of lymphoid tissue. Subacute catarrh.

Stomach.—Subacute catarrhal gastritis. Atrophy. Small plasma-cell infiltrations in subserosa.

Adrenals.—Patches of lipoidosis in cortex. Increased pigmentation. Small active syphilitic infiltrations in medulla.

Kidneys.—Subacute parenchymatous degenerative nephritis with ascending purulent pyelonephritis.

Seminal Vesicles.—Marked pigmentation of epithelium. Hyaline thickening of walls.

Testis.—Simple atrophy. Aspermatogenesis. Early syphilitic orchitis, more advanced in left.

LEVADITI PREPARATIONS

Levaditi preparations were made of the wall of the aneurysmal sac and of portions of the pulmonary artery below the aneurysm. As the autopsy was performed nine hours after death the conditions were not regarded favorable for a successful Levaditi, although the internal organs were still warm. In five out of fifty sections of the aneurysmal wall undoubted spirochetes of the pallida type were found. In one section three spirochetes were found in the fresh blood clot in the sac, showing the occurrence of the organism in the circulating blood. They were also found in small groups, 3 to 5, in the wall of the sac, towards the adventitia. In the wall of the pulmonary artery they were also found in small groups in the same location. Owing to the length of time postmortem the fixation and impregnation were not as good as we desire; and as no one of the spirochetes lay wholly within one plane the photomicrograph shows only portions of the organisms in one plane.

Pathologic Diagnosis.—Syphilis. Syphilitic aneurysm of left upper division of left pulmonary artery. Hemorrhage into lung. Brown induration and edema of lungs. Syphilitic pulmonary arteritis, aortitis, myocarditis, hepatitis, pancreatitis, adrenalitis, orchitis, lymphadenitis, etc. Multiple gummata of liver. Subacute parenchymatous nephritis with purulent ascending pyelonephritis. Old tubercle in right lung. Anemia. Terminal acute pericarditis. General sclerosis and atrophy.

Summary and Conclusions.—Up to the present time no positive pathologic evidence of the existence of a syphilitic atherosclerosis of the pulmonary artery has been produced. This case offers such positive evidence; and syphilis of the pulmonary artery is now put upon the same basis as that of the aorta. The microscopic changes in the atherosclerotic pulmonary artery of this case show exactly similar changes to those found in the wall of definitely recognized syphilitic aortas. Given sections of this pulmonary vessel can not be distinguished microscopically from given sections of syphilitic aortas. The evidence here speaks decidedly in favor of the view of the specific nature of this especial form of arterial change. From the writer's experience he believes that *atherosclerosis, either of the ordinary type or of the syphilitic type macroscopically, that shows on*

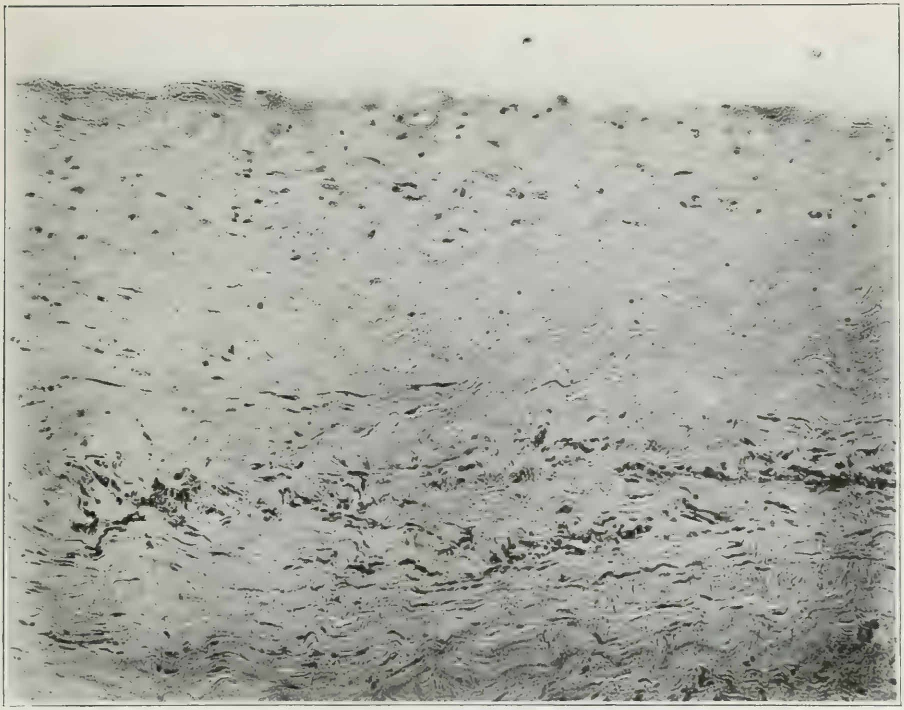

Fig. 7.—Wall of aneurysm of upper branch of left pulmonary artery. Marked fibrosis and hyaline change of intima and media. In the latter small lymphocyte and plasma cell infiltrations about the small vasa vasorum.

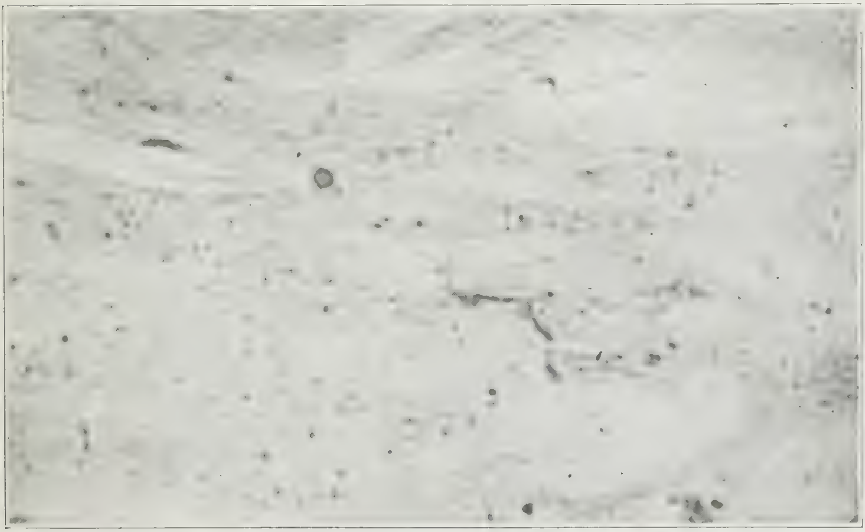

Fig. 8.—Levaditi preparation of wall of sclerotic pulmonary artery. Portions of six spirochetes are seen in the photograph, three near the center field, one at top, one in upper left, and one in left. The two in central field show fairly well. It was impossible to find any spirochetes lying wholly within one focal plane; and these were the only two in which several turns of the organism could be shown in the same focal plane. This field showed unfortunately some precipitate.

microscopic examination perivascular infiltrations of lymphocytes and plasma cells along the course of the vasa vasorum, most marked in the adventitia; and following the vessels in their course through the media towards the intima, with obliteration of the arterioles, new formation of capillaries, fibroblastic proliferation, fibrosis of intima and media, secondary hyaline change and atheroma is specific in character, and is due to the localization of spirochete pallida along the vasa vasorum.

Macroscopically the picture presented by the affected artery may be that of ordinary atherosclerosis or of the type recognized at the present time as syphilitic mesaortitis. Syphilis can not be ruled out by the naked-eye appearances of the aorta or artery at the autopsy table; the autopsy diagnosis of syphilis, however, can be made on the macroscopic criteria of syphilitic mesaortitis, as given above. Aortas presenting the gross picture of atherosclerosis may show on microscopic examination the most marked syphilitic infiltrations of the media and adventitia, and in Levaditi blocks from the same the presence of spirochetes has been shown. *The microscopic examination is the only method by which syphilis of a vessel can be determined; macroscopic appearances can not be relied upon.*

The gross appearances of the pulmonary artery in this case were those of atherosclerosis. Had it not been for the aneurysm present its syphilitic nature would not have been sought and demonstrated. The question, therefore, of great importance now is the frequency of syphilitic lesions of this artery. Is it rare, as Winternitz and Schmeisser conclude? Probably not, as a part of the general picture of old syphilis. Many of the slight or moderate scleroses of this artery found at autopsy may prove on histologic study to show active syphilitic infiltrations. These alone could be safely interpreted as syphilitic. Future studies must be relied upon to give us knowledge as to the incidence of syphilitic lesions of the pulmonary and other arteries.

That syphilis of the pulmonary artery and its branches is of great clinical importance does not appear at the present time. In our case it was, being the direct cause of the symptoms and chiefly responsible for the death of the patient. This was due to the fact that the syphilitic disease of the artery had led to the production of an aneurysm of such size as to be of clinical importance; but syphilitic aneurysm of the pulmonary artery would appear to be a very great rarity from the literature. It is most probable that in every case of syphilis some lesions occur in the pulmonary artery as they do in the aorta; but their clinical significance would be probably only that of a contributory factor to the general cardiovascular disturbances that arise sooner or later in every one who has become infected with syphilis. There is, however, a distinct clinical complex of dyspnea, cyanosis, cardiac enlargement, chronic passive congestion and polycythemia that has been shown in a small number of cases (Mönckeberg, Romberg, Aust, Rogers, Sanders, and Barlaro) to be associated with a marked sclerosis of the pulmonary artery. Barlaro has recently reported a case of this kind in a woman of 44 years. The chief symptoms were marked cyanosis, pulse 80, regular, right heart dilated, red cell count, 6,680,000, attacks of dyspnea about three times daily relieved by expectoration which occasionally gave bloody sputum, general chilliness and coldness of feet. Barlaro calls this condition "Ayerza's disease," and believes that some of the cases reported as chronic polycythemia, "Vaquez's disease," were of this type. He believes that syphilis is probably the etiologic factor. In a case of chronic cyanosis, polycythemia (9,000,000 red cells) and dyspnea, autopsied by the writer a few years ago he found the most marked condition of atherosclerosis of the pulmonary artery and branches. He thought the polycythemia might be purely compensatory for the pulmonary sclerosis. This case is under study and will be reported later.

In conclusion, this case presents a patient with definite history of chancre and skin rashes, with Wassermann + – – –, showing at autopsy syphilitic lesions in heart, aorta, liver, pancreas, adrenals, and testes, and an atherosclerosis and aneurysm of the pulmonary artery in the walls of which *spirochete pallida* was demonstrated. Syphilis of the pulmonary artery and syphilitic aneurysm of the pulmonary artery are, therefore, for the first time conclusively demonstrated as pathologic entities.

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The Pathology of Gassing with a Bibliography Upon the Medical Aspects of Gassing

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THE PATHOLOGY OF GASSING WITH A BIBLIOGRAPHY UPON THE MEDICAL ASPECTS OF GASSING

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A large and almost entirely new field of pathology has been opened up by the modern use of poisonous gases in warfare. Until the deliberate and studied adoption of this means of attack by the Germans in April, 1915, most of the types of gassing, which have now become all too common, were known only through the rare occurrence of laboratory and industrial accidents. Some of them, induced by hitherto little known organic compounds, are without precedent in pre-war medical literature. But now research in the pathology of these conditions has come to be not alone a matter of scientific interest, but an absolute necessity to the successful conduct of the war.

The literature upon the pathology of gassing is, for the greater part, characteristic of the mass of material which has accrued to each of the important medical aspects of the war. As will be seen in this short review and the accompanying bibliography, the published work directly and indirectly concerned with this subject has already become voluminous, comprising considerably more than one hundred titles. Unfortunately, however, relatively few of these articles contribute materially to an exact understanding of the lesions produced by the various agents employed in military gassing. The reasons for this are obvious and sufficient. In the emotional stress and strain of the first gas attacks in Flanders, all attention was rightly turned toward means of alleviation and protection, and these considerations, together with the highly colored but none too scientific descriptions of the refined tortures there witnessed, fill the articles of that period. The rapid progress made in elaborating the method of the gas attacks with the frequent changes in the agent used, seemed to leave little time or opportunity for approaching the problem either by the experimental method or through the careful study of the gross and microscopical changes found at autopsy. Uncertainty as to the identity of the gas causing the particular casualties in question has rendered many of the case reports of little value and the fact that a mixture of irritative and asphyxiative gases rather than a single substance has usually been employed has introduced much confusion in attempting to assign to components of the mixture precise causative effects. Still another reason for the somewhat disappointing character of this literature, considered as a whole, has been the military necessity of withholding from publication, for a time, at least, data concerning the character of the gases used on certain occasions and the morbidity and mortality produced by them. Notwithstanding these handicaps a number of excellent papers have already appeared and the general adoption of the experimental method in attacking this problem promises much for the future.

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The use of cloud or drift gas and of charged explosive shells, bombs, grenades, etc., are the two methods by means of which gassing is usually accomplished. The first of these, although singularly successful when first employed, is in reality strictly limited in its application since only those gases which are considerably heavier than air and which can be provided in enormous quantities can be thus employed. Its use is likewise dependent upon favoring atmospheric and topographical conditions. None of these factors is concerned in the dissemination of poisonous gases by means of charged shells and grenades, so that this method is available at all times for a very large number of gases and volatile liquids. In addition, gassing, as it occurs in warfare may be brought about by a number of other methods. In military mines it may occur from exposure to either nitrous fumes or carbon monoxide generated in previous explosions in the same area. Sundell (80) states that in the area with which he was familiar more casualties occurred during the few days subsequent to the explosion of a hostile mine than at the time of the explosion itself. The carbon monoxide permeated the friable chalky soil or was confined in fissures produced by the explosion only to be released by fresh workings or puffed out into the mine by the settling of the soil. In naval warfare (Carpenter (56)), likewise, gassing is an important factor and here the chief hazards are from smoke and explosion gases. These may be derived from fires starting below deck, from funnel smoke entering pierced ventilators and thus reaching all parts of the ship, from the bursting charges of exploding enemy shells, from the powder gases of the ship's own guns, or even from overheated lacquer and paint on turret guns (in the U. S. navy the breaches of the guns are unpainted). The transportation of troops by automobile has introduced still another gassing hazard and accidents similar to the garage deaths of civil life are met with. Such a case is described by Teynac (81). Eight officers who were being transported in a closed automobile from one sector to another were found unconscious on the floor of the vehicle at the end of the three and one half hour journey. It was subsequently shown that exhaust gases could enter the enclosed compartment through the floor. In this instance all of those overcome eventually recovered. In both France and Germany soldiers have been poisoned by arsine, produced as an impurity in the generation of hydrogen for filling balloons (Cevidalli (57)).

Lists of the gases used in the present war have been compiled by Hill (20), Cevidalli (57), Gallo (66), Filippini (64), and others. Some of these authors have included with gases known to have been used, others said to have been used but not yet verified. The list given by Vaughan (106) is the most recent and complete for it includes many of the organic compounds which have played so large a part in the past year. Those gases and volatile liquids known to have been used include chlorine, phosgene, hydrocyanic acid, phosphine, arsine, hydrosulphuric acid, dichlorethyl-sulphid (mustard gas), chloropicrine, acroleine, methylchloro-sulphate, bromide of benzyl, chloracetone, bromacetone, iodacetone, bromacetic ether and iodacetic ether. Others, the use of which has been less authentically stated or implied are nitrogen peroxide, carbon monoxide, sulphur dioxide, bromine, cyanogen, arsenic trichloride and phosphorus trichloride. Regardless of their intentional use as gassing agents, carbon monoxide and nitrous fumes have to be considered because of their production as explosion gases and as products of the burning of explosives without detonation. In the open there can be but little danger from these two, but in military mines and underground shelters they play an important part.

The pathology of many of the gases above mentioned is at present understood only in the most general way and attempts to group them according to similarity of action are far from satisfactory. Arsine, phosphine, hydrocyanic and hydrosulphuric acids are known to cause death directly, that is, by virtue of their intrinsic toxicity. On the other hand, chlorine, phosgene and many others are more commonly described as causing an asphyxiative death by reason of pulmonary changes. As will be seen, however, there are many reasons for thinking that this is but a matter of degree and that death may be as direct and almost as immediate after chlorine gassing as after hydrocyanic acid. Similarly, those gases which are characterized by their lacrymatory effect and are thus grouped together are in some instances extreme respiratory tract irritants as well, and in sufficient concentration may produce an asphyxiative death through pulmonary oedema. The so-called mustard gas has both of these properties, but is still more notorious by reason of the skin lesions which it produces by direct contact. It will thus be seen that for the present the pathology of gassing can be considered only from the standpoint of the lesions produced by individual gases.

CHLORINE. Chlorine has a density of 2.450, is liquid at ordinary temperatures under relatively low pressure and is highly irrespirable. It is therefore well suited to use as a cloud or drift gas. Klotz (90) found that a concentration as low as 1 part in 10,000 would produce acute poisoning in small animals. Filippini (64) gives .05% as a fatal concentration while one of .4% to .6% produces speedy death. In experimental animals death may be produced within one to two minutes with higher percentages.

The symptomatology and pathology of chlorine gassing depend entirely upon the concentration of the gas and the duration of exposure to it. All show from the first the most intense irritation of the respiratory mucous membranes with incessant coughing. Those most severely affected die in the trenches within a few minutes, with or without haemoptysis, and when found have a faint greenish yellow appearance like that of asphyxia pallida (Bradford & Elliott (6)). The literature affords no record of post mortem findings in these immediately fatal cases. In dogs similarly poisoned, the peripheral vessels do not bleed at autopsy and the lungs are found to be shrunken, dry, bloodless and friable. Men who survive the attack for a few hours develop the most intense acute pulmonary oedema with extreme cyanosis, dyspnoea and very abundant frothy expectoration, often blood tinged. Most of the deaths occur in this stage. Autopsies of cases dying during this asphyxial stage show (Black, Glenny & McNee (5), Henry (18), and others) a well marked inflammation of the pharynx and larynx without membrane formation, intense congestion and oedema of the trachea and larger bronchi, and a most extraordinary oedema of the lungs such that the patient has literally drowned in his own body fluids. Sub-pleural haemorrhages are practically always present, evidence of the essentially asphyxiative character of the death. Sub-epicardial and sub-endocardial haemorrhages may also be present. Intervesicular emphysema is common and mediastinal emphysema by no means rare. In 7% of the cases (Sisto (79)), there is a sub-cutaneous emphysema appearing at the base of the neck and spreading over the anterior surface of the thorax, reaching eventually to the abdomen and scrotum. The heart is dilated, particularly on the right side. All abdominal organs show marked passive congestion. The stomach in all cases shows a marked catarrh and in most cases sub-mucous haemorrhages.

As the intense oedema disappears, the frothy sputum gradually becomes more purulent and a severe muco-purulent bronchitis develops. In this stage the damaged lung tissue is especially open to bacterial invasion and pulmonary gangrene or pneumonia may terminate the picture. Those who have been severely gassed with chlorine, recover but slowly and for months are dyspnoeic and cyanotic on slight exertion. Just what the reparative processes may be in these cases is not yet known but it seems probable that there is marked increase in the fibrous connective tissue of the lung and that the more severe cases undergo to some extent an obliterative bronchiolitis.

As the most striking feature, both of the symptomatology and of the gross pathology of chlorine gassing, the pulmonary oedema has aroused much interest. Its appearance is so rapid that it scarcely seems possible that it could be purely inflammatory in character. According to Hill (20), the exudation follows directly upon, and as a result of, the injury to the surface epithelium and underlying capillaries and he cites experimental evidence in support of his belief. Schäfer (42), on the contrary, by a series of elaborate studies on cats, rabbits and dogs came to the conclusion that chlorine produces its fatal results by causing obstruction of the pulmonary vessels, amounting in some cases to complete stasis. He also called attention to the vicious circle between oedema and vascular obstruction.

This conclusion of Schäfer's has been supported and explained by observations upon the blood and circulatory changes in chlorine gassing, which, taken as whole, represent the most important advance that has been made in the pathology of gassing. It has been repeatedly noted that the blood of chlorine gassed patients coagulates with great rapidity. So marked is this change that therapeutic blood-letting is oftentimes a matter of much difficulty. The dark colored, thick, viscid blood flowing sluggishly from even large veins is frequently described. Pulmonary thromboses and infarction are also noted in the earlier autopsy reports but no great stress is laid upon their importance, yet thromboses elsewhere in the body are mentioned in case reports with significant frequency. For instance: Giroux (13), describes a case of hemiplegia consequent to chlorine gassing which he attributes to the thrombosing action of chlorine; Sisto (79), notes thrombosis of a brachial artery; Bradford and Elliott (6), record three cases with vascular obstruction in the lower extremities, with progressive loss of the arterial pulse, coldness and lividity of the limb and threatened gangrene; Kramer's (91) case showed pulmonary and coronary thrombosis together with a parietal thrombus of the left ventricle; Boldireff (83), warns that there must be no rubbing of the gassed patient in order to warm him as this is liable to induce embolism. Pozhariski (39), finds that among the severe changes, noted in cases dying in the first twelve hours after chlorine gassing, is the marked increase in the coagulability of the blood rendering it thick and unable to circulate freely. He finds white thrombi in many cases and concludes that the blood changes and thrombus formation so embarrass the work of the heart that tissue asphyxia results. He further states that embolism and infarction are to be expected among the complications.

Hake (15) investigated the direct action of chlorine upon the blood *in vitro,* but the conditions of his work were not such as to throw light upon the factor of coagulability. He did find, however, that the characteristic dark bands of the oxyhemoglobin absorption spectrum, as obtained in dilute blood, are discharged by adding chlorine water drop by drop and that if chlorine gas is allowed to bubble through dilute blood, the iron of the hemoglobin, at least in part, passes into solution in the colorless filtrate and can be there demonstrated by the usual tests. He calls attention to this permanent destruction of the hemoglobin as a possible explanation of the immediately fatal cases of chlorine gassing, since this change if it takes place in the human body would be more serious even than the more or less temporary fixations of carbon monoxide and cyanogen with hemoglobin.

The recently published work of Klotz (90) is an important contribution to the study of the blood changes in chlorine gassing. He finds that in severely and fatally gassed animals there is microscopical evidence of coagulation within the dilated capillaries. While this may be the result of the abstraction of fluid, as may also be the increased viscosity of the blood, it seems more probable that the local and direct effect of the chlorine hastens coagulation for he shows that human blood in an atmosphere of 1-1000 chlorine coagulates in about 15 seconds and more rapidly in stronger concentrations. He does not, however, assign this as the sole reason for the acute deaths. "It would appear that the acute deaths of the experimental animals were the direct result of obstruction of the pulmonary circulation and that the presence of the pulmonary oedema was a factor in this regard." If the individual lives somewhat longer, the fatal result is more particularly associated with the oedema.

It will thus be seen that the most important action of chlorine is, perhaps, its power to lower the coagulation time of the blood. If further experimental work supports this view, it will completely alter all former conceptions of the pathology of chlorine gassing. As a working hypothesis, it explains the immediate deaths; the dry and almost bloodless condition of the lungs in animals gassed with rather high concentrations; the initiation of the vicious circle which includes pulmonary stasis, pulmonary oedema and cardiac dilatation; and the thrombosis, infarction, embolism and multiple haemorrhages which are part of the clinical picture.

The changes in the cellular elements of the blood are apparently not important. The erythrocyte count, as reported, is usually about normal although the concentration of the blood by the extreme pulmonary oedema must be remembered. Evidence of a slight hemolytic icterus has been given in a few case reports, but hemolysis does not play any great part. Heitz (16) quotes below that the hemoglobin reading of fifteen subjects examined on the eighth to eleventh day averaged 100%. The white cells in this same series of cases ranged from 7000-10,000. Miller (97) finds that a case which has been gassed sufficiently severely to produce symptoms lasting for some time shows a more or less marked relative lymphocytosis which takes some time to develop, three to four months, at least. This he attributes to chronic inflammatory changes in the lung.

The gastro-intestinal lesions in chlorine gassing are also important. Acute epigastric pain, with vomiting, oftentimes bloody, is very frequently one of the early manifestations. Altered blood may be vomited for several days following the gas attack and those who have been at all seriously affected usually show anorexia and intolerance of food. Leoper, Peytel and Sabadini (30) describe cases which had unmistakable signs of a severe erosive gastritis, eventually relieved by bicarbonate of soda and a milk diet. Reference has already been made to the post mortem changes in the stomach; congestion, petechial haemorrhages, patches of bloody suffusion and in some cases ulcerations. Bradford and Elliott (6) found the stomach full of blood in two out of sixteen autopsies. Similar but less marked changes have been described for the duodenum. Sergent and Agnel (43) attribute the gastric changes to local caustic action from swallowing the gas. They are more probably asphyxiative, embolic or thrombotic.

In regard to changes in the central nervous system Neiding (100) states that of 274 cases of drift gas poisoning (probably chlorine but possibly chlorine combined with phosgene) more than 50% presented objective nervous manifestations. The headache and feeling of extreme fatigue are considered by Bradford and Elliott (6) as signs of toxic lesions of the central nervous system but they found no gross changes in the brain at autopsy. Miliary haemorrhages are described by several but they seem to be a much less constant finding in chlorine than in phosgene poisoning.

Chlorine gassing does not produce characteristic parenchymatous changes in either liver or kidneys. Surprisingly few cases have shown albuminuria. After the first week the percentage is higher but this is doubtless to be attributed to the advent of pulmonary infections. Bradford and Elliott (6) found that in all men dying in the second week the kidneys showed the changes of a moderate acute parenchymatous nephritis, yet none of them had had oedema and only one uraemic symptoms; and the authors emphasize the usual absence of albumin and casts in their gassed cases.

Sergent and Agnel (43) suggest that the feeling of general weakness, the great fatigue, the hypotension and fall of temperature call to mind the phenomena of suprarenal insufficiency. Voivenal and Martin (107) insist that gassed cases show a suprarenalitis with insufficiency. There is, however, no gross or microscopical evidence of structural changes in the adrenal in cases known to be due to uncomplicated chlorine poisoning.

PHOSGENE. $COCl_2$, carbonyl-chlorid. Phosgene is a liquid which boils at 8.2° giving off a colorless gas which is exceedingly suffocating and irritative. The density of the gas is 3.49 as compared to air. It is used both as a shell gas and a drift gas, in the latter case usually mixed with nine parts of chlorine.

Phosgene poisoning closely resembles chlorine poisoning but is considered by all as being more serious. Vaughan (106) says that phosgene is twenty-four times as effective as chlorine and Filippini (64) gives 0.25% as a concentration which is rapidly fatal. The toxic action has been attributed to carbon monoxide produced by decomposition in the presence of water according to the formula,—

$$2\ COCl_2 + H_2O = 2\ CO + 4\ HCl + 2\ O.$$

but this is probably not the true explanation.

The pre-war literature dealing with the lesions of phosgene poisoning has been reviewed by Filippini (64). He cites the cases of Müller and of Roos as reported by Bilancioni. One of Müller's cases came to autopsy showing a marked dilatation of all the chambers of the heart. The five cases of Roos showed in life, cough, cardiac dilatation, weak pulse, marked cyanosis, polycythemia, marked leucocytosis with lymphopenia, and albumin, indican, urobilin and casts in the urine. Autopsy of the two cases which died showed focal pneumonia, sub-pleural haemorrhages, acute bronchitis, multiple thromboses of the pulmonary arteries, fatty degeneration of liver and spleen, and minute thromboses of cerebral and intestinal vessels.

In experimental phosgene gassing of rabbits and cats Bilancioni (54) found the most severe contact lesions, the mucosa of larynx, trachea and larger bronchi being in a state of necrobiosis and desquamating in large strips. There was marked pulmonary oedema and congestion with thromboses and haemorrhagic infarctions. In some cases the intrinsic laryngeal muscles showed fragmentation, which he thinks may have been due to, or favored by, the convulsive opening and closing of the larynx. The laryngeal lesions, particularly the haemorrhages into the sub-mucosa, and the extreme pulmonary oedema he considers the most important features.

Similar pulmonary lesions are found in the human cases, and the occurrence of thromboses is also repeatedly mentioned. The Italian writers emphasize the frequency of thrombosis of mesenteric vessels resulting in some cases in a diffuse necrotic enteritis and localized peritonitis. Punctiform haemorrhages in the brain are also a frequent finding. These are considered by Mott (98) as of embolic origin, possibly due to pigment granules of altered hemoglobin. In the brains of two cases of drift gas poisoning he found the white matter peppered with innumerable haemorrhages, each about the size of a pin head. These were microscopically like those of carbon monoxide poisoning except that the haemoglobin appeared to have been largely converted into chocolate colored granules, a change which he thinks may have been due to the action of hydrochloric acid, liberated from the phosgene, in converting the haemoglobin into acid haematin.

Bromine. Density as compared to air, 5.52. Boiling point, 59°. Although organic bromine compounds are now being used extensively, there is little evidence in the literature to indicate that bromine itself has ever been employed. Animal experimentation has been carried on with it in this connection, however, to an extent second only to that in the case of chlorine. Symes (46), and Symes and Golla (47), using a high concentration of bromine vapor on pithed cats, found a marked obstruction of the air-way which they believed to be due in part to spasm of the bronchial musculature. Failing to relieve this by intravenous use of atropine, although the inhalation of stramonium fumes was consistently successful, they concluded that the bronchial circulation had been obstructed to such a degree that the muscle could be reached by local application only. This is of great interest in connection with circulatory obstruction in those severely gassed with chlorine. Hill (20) found that bromine vapor in a 1-1000 concentration killed the mucous membrane of the trachea so that it might be stripped off by violence of the respiratory efforts and be drawn into the larger bronchi, forming a tree-like cast which suffocated the animal. In general, bromine resembles chlorine in its action, but is much more irritating to the conjunctiva and the mucosa of the upper respiratory tract, while there is reason for believing that the pulmonary changes are not quite as marked. If used in warfare as a shell gas, the well known cutaneous lesions would be an important part of the pathological complex.

Hydrocyanic Acid. HCN. Clear liquid, boiling at 26°. Density as a gas, 0.948 compared to air. Hydrocyanic acid is being used intensively as a shell gas. Its boiling point is such that it is well adapted to this use. Its direct and immediately lethal toxicity as well as the practical absence of anatomic lesions are well known, and its use in warfare has thus far produced nothing new in this regard.

Hydrosulphuric Acid. H_2S. Colorless gas of characteristic odor. Density compared to air, 1.191. Gaseous at all ordinary temperatures and pressures. Other than reports of its use, little information in regard to poisoning with hydrosulphuric acid gas has appeared in the war literature. Filippini (64) says that death may follow its inhalation at a concentration of but .07-.08 per cent, if continued for some time, and that 1,5-2.0 per cent is rapidly fatal.

Phosphine. PH_3, density 1.214, and Arsine, AsH_3, density 2.695, have both been used in warfare. The lethal concentration of the former is given as 0.025%. It kills directly by virtue of its own toxicity. In addition to its use as a weapon of offense, arsine assumes some importance as a source of accidental gassing. This possibility in connection with the generation of hydrogen for filling balloons has already been mentioned. It has also been reported as one of the many hazards to which the crews of submarines are exposed. In arsine gassing, death is usually delayed, occurring from the second to the sixth day. Extreme hemolysis, icterus, haematuria and prostration dominate the clinical picture.

SULPHUR DIOXIDE. SO_2. Density, 2.21. Sulphur dioxide is easily liquefied by cold and pressure and has been used, according to Lung (31), in hand grenades, filled with the liquid and provided with a small bursting charge to scatter the contents when thrown. It is a respiratory irritant and in sufficient concentration produces pulmonary lesions and asphyxia. It is not effective unless comparatively concentrated and apparently has not been much used as it is mentioned by but a few authors.

NITROUS FUMES. N_2O_3, nitrous anhydride, density 2.63; and NO_2, nitrogen peroxide, density 1.57. In the first few months of the gas attacks many writers believed, probably incorrectly, that the oxides of nitrogen were being used. There was little to support this view and nitrogen compounds are too valuable to be used in this manner, but the oxides are nevertheless important as detonation gases from many of the high explosives now used. This hazard is also met with in civil life as described by Watt and Irvine (51) for the Transvaal mines, where burning blasting gelatin produces these fumes. One of the most characteristic features of nitrogen peroxide poisoning is its delayed action. Hill (20) calls attention to the fact that firemen exposed to the fumes of nitric acid are unaffected at the time but develop a fatal inflammation of the lungs during the next twelve hours. Gassing with nitrous oxides as it occurs on board ship is discussed by Ohnesorg (72) in a review of the work of Esch. There is usually a little headache, cough and tightness of the chest which soon passes off. Then in six to eight hours there is dyspnoea, cough, bloody serous expectoration and death from asphyxia and heart failure occurs in about forty-eight hours. At autopsy there are found pulmonary congestion, oedema, and marked inflammation of the mucosa of the trachea and larger bronchi. A bronchiolitis obliterans may develop in the lungs of those not fatally gassed.

CARBON MONOXIDE. CO. Density, 0.9678. Like nitrous fumes, carbon monoxide was thought by many to have been one of the gases used in the early attacks. Its lightness and the fact that it can be liquefied only by extremes of temperature and pressure make it entirely unsuited to use as either a cloud or shell gas. Its importance, as mentioned above, is due to its production in enormous quantities as a detonation gas. Readily diffused in the open, it becomes exceedingly dangerous when encountered in military mining. It can be readily detected, even in minute quantity, by the use of mice or canary birds, which are susceptible to about 0.05 to 0.06%. Breathing of otherwise normal air containing 0.2% of CO for several hours will usually cause death and 0.1% may be fatal through cumulative action. Basing his report upon cases due to carbon monoxide gassing in military mines Sundell (80) gives a very good description of the clinical picture. The premonitory symptoms are heaviness and loss of power in the limbs and giddiness or light-headedness. The loss of power of the extremities may be so marked that the victims are unable to escape although conscious that they are being overcome, or they may fall from the ladders in trying to climb out of the mine. He notes that these men usually show pallor rather than the classical pink color. Vomiting is an almost constant symptom and headache usually comes on when the men are brought out to the fresh air. In the non-fatal cases this is a very persistent symptom. At autopsy the chief, and often the sole, lesions are punctate cerebral haemorrhages sometimes with ecchymoses in the meninges. Through this finding, the pathology of carbon monoxide poisoning makes contact with that of shell shock, the occurrence of similar haemorrhages in shell shock having raised the question of a common etiology. This problem has been investigated by Mott (98) and others.

CHLOROPICRINE, ACROLEINE, DIBROMACETONE, METHYLCHLORO-SULPHATE and probably other organic compounds (Vaughan (106), Filippini (64)) have been used for their lethal effect. The literature as yet gives no detailed discussion of their pathology. In general, they are irritants to conjunctival and respiratory mucosae and probably produce an asphyxial death through pulmonary oedema.

BROMIDE OF BENZYL, MONOCHLORACETONE, BROMACETONE, IODACETONE, BROMACETIC ETHER, IODACETIC ETHER, and other compounds are used primarily for their lacrymatory effect. Between this group and the preceding no sharp line can be drawn. The lacrymatory gases are usually liquids at ordinary temperatures and are scattered from shells and hand grenades. The heat of explosion probably suffices to vaporize the liquid as the boiling points of most of these substances range between 110° and 130° (Filippini (64)). Concentrations of some of the bromine compounds as low as one part in several millions are said by Hill (20) to render men ineffective through lacrymation and photophobia. There are several articles dealing with the lesions produced by unidentified members of this group but this is otherwise an un-worked field. Trémolières and Loew (1) report upon five soldiers gassed with shells which gave off a heavy, acrid, suffocating yellowish smoke. They felt a severe smarting compelling them to close their eyes, and sharp pain in the throat with violent cough. They felt stupefied and two lost consciousness. In the open air, they revived but continued to have constant lacrymation and photophobia. After several hours sight was obscured and they believed themselves blind. Three had watery greenish vomitus. When seen about thirty-six hours after gassing there was intense congestion of bulbar and palpebral conjunctivae, constant lacrymation and a marked opacity of the cornea so that fingers could be counted only with great difficulty. Purulent bronchitis and broncho-pneumonia developed. There was constant cough and the greenish yellow purulent sputum was often blood streaked. All suffered profound psychical and physical depression. The blood count showed the red cells moderately reduced in number, the leucocytes increased. There were some nucleated reds and coagulation was rapid. At no time were there albumin, sugar or bile pigments in the urine. These patients all recovered, the lung signs clearing up in ten days to three weeks and eventually the corneal opacity likewise disappeared, leaving normal vision. The authors note the reduction of the red blood cells without haemoglobinuria or haemolytic icterus as an interesting feature of these cases. Agasse-Lafont and Roux (82) report another group of cases gassed by an unidentified lacrymatory gas. All of the five men under observation had persistent vomiting after each meal for several days and then developed all the symptoms of gastric erosion or ulcer. One vomited blood on two occasions. Another had melaena and the erosion seemed to be in the duodenum. Gastro-enterostomy was done in this case and all symptoms subsided. These case reports suggest vascular or haemic changes similar to those found in phosgene gassing.

"MUSTARD GAS," DICHLORETHYLSULPHIDE. The so-called mustard gas has been in use by the Germans since July, 1917. It is used entirely by means of shells and is scattered in liquid form by the bursting charge. It requires special mention since it produces the most severe chemical burns as well as being lacrymogenous and a respiratory irritant. The following data are largely taken from Mandel and Gibson (95). A slight odor of mustard is experienced at the time of gassing but little else. After a free period of from four to sixteen hours, during which the patient usually continues his duties, there is epigastric distress and violent vomiting. The cardinal symptoms are (1) conjunctivitis, photophobia and lacrymation,* (2) irritative laryngitis and bronchitis, persistent cough, serous to haemorrhagic expectoration; (3) burns of hands, face, genitals, buttocks, shoulders and back. In the less severe cases, the skin may be merely pigmented, brownish black, and harsh to the touch. Later this will be followed by desquamation. More often there is distinct blistering with vesicles varying in size from that of a millet seed up to 4 or 5 inches in diameter. Second degree burns are not uncommon. (Through a personal communication the writer has learned of a chemist who received a deeply sloughing burn from a drop of dilute solution of this liquid running across the back of the hand although the accident was observed and the hand promptly washed.) In severe cases of gassing with "mustard gas" death may occur early from pulmonary oedema. Bronchopneumonia is the most common complication. Albuminuria is not uncommon but true nephritis extremely rare.

From this survey of the literature it will be seen that the pathology of gassing, particularly as applied to the chemical warfare of the past twelve months in which little known organic compounds play the chief part, has yet to be written. The action of each of these organic compounds is a problem in itself which can be properly approached only from the experimental standpoint. The rapidity with which this is done may be the limiting factor in developing a rational therapy.

The accompanying bibliography comprises as far as possible all the important titles on gassing in modern warfare including those which deal with prevention and treatment as well as with symptomatology and pathology. About sixty titles have been omitted. These are chiefly editorial notes, short reviews or popular articles of no scientific value. On the other hand, about fifty references not found in the bibliography distributed from Washington are included in this list.

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NOTE ON FATTY EMBOLISM AND SHOCK

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THE RELATIONSHIP OF FAT EMBOLISM TO TRAUMATIC SHOCK.

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In 1913 the writer published in the International Clinics, Vol. 4, S. 23, 57 pp., a very complete monograph on "Traumatic Lipaemia and Fatty Embolism." The material for this work had been put together in 1907 for publication in book form, but such publication had been deferred. The leading facts of the article, however, have been used in the author's teaching work for more than ten years, and were applied at the beginning of the War in special courses on War Pathology to the conditions resulting from bone fractures received in warfare. Therefore the recent publication by the *Atlantic Monthly Press* of William Townsend Porter's "wonderful discovery" that fat embolism of the pulmonary capillaries "is a frequent, if not the most frequent, cause of shock as seen on the battle-field" deserves a critical review because of the ignorance or the deliberate ignoring of the literature of American medical science shown in this *literary* article. The offense is the greater because the author of "Shock at the Front" makes it clear that his work was carried out, and evidently published, under the auspices of the Rockefeller Institute for Medical Research. Porter's discovery is revealed in paragraphs scattered through a Atlantic Monthly literary setting, as follows:

Page 44.—"The Surgeons at Compiegne had noticed that shock came on chiefly after wounds of the great bones, such as the thigh-bone, and after multiple wounds through the skin and subcutaneous fat, as from a shower of shell-fragments. These facts seemed very significant, although I little knew at the time that they would at length lead me to the discovery of the cause of shock."

Page 93.—"I could not rest, I was still pursued by the imperious fact that shock was most frequent after fractures and after multiple wounds through the subcutaneous fat. I took refuge in my laboratory, in experiment after experiment. The cause of shock was found, and a new remedy."

Page 95.—"Since the fracture of the bone is apparently a factor in shock, and since the absorption of a chemical substance was excluded, the mischief might be due to a mechanical agent. Now, the bone-marrow is very rich in fat, and it has long been known that after fractures of the femur large numbers of fat-globules appear in the blood, in which the globules circulate until they enter the capillaries in the brain and other organs. When a large fat-globule enters one of these small, hair-like vessels, it sticks fast, the blood can no longer flow through that capillary, and the cells supplied by that blood can no longer get food and oxygen.

"All this is well understood. For more than two centuries observations have been made by pathologists on changes in the tissues, following the injection of fat into the blood-vessels of animals.* Indeed a condition suggesting shock has incidentally been observed here and there in the course of these studies, although I did not know of these chance observations until long after my own experiments. No one, however, had declared or attempted to prove that the entrance of fat into the blood-vessels was the cause of shock as seen on the battle-field. The pathologists were after other game. They were interested in the anatomical changes in the tissues following the blocking of the capillaries. Since a falling blood-pressure is the out-standing symptom of shock, the proof demanded (1) that fat-globules should be injected into the vessels; (2) that the blood-pressure should be measured; (3) that the blood-pressure should fall gradually as it does in shock; (4) that the other symptoms seen in wounded soldiers should be accurately reproduced in the injected animal. The other symptoms are a feeble and rapid heart-beat, frequent and shallow respiration, pallor, low temperature, diminished sensibility and apparent unconsciousness.

"On February 2, 1917, the crucial experiment was made. An instrument for recording the blood-pressure in the carotid artery of an anaesthetized cat was arranged to write its record on a moving surface of smoked paper. When the normal pressure was in record, a little less than a teaspoonful of olive oil was injected into the jugular vein. Thereupon the blood-pressure began to fall, and the animal soon showed all the phenomena of shock observed in the wounded soldier.

"My attention was then directed to the discovery of a new remedy. Following the plugging of the capillaries by fat the arteries and heart are partially emptied, and the blood collects in the veins, especially in the large and numerous abdominal veins. In fact, the patient may be said to bleed to death in his own veins since the quantity of blood left in the arteries does not suffice for the nutrition of the cells of the brain and other organs."

Porter then proposes briefly remedies for the condition, such as changing the physical condition of the fat emboli, draining the blood from the veins by means of the respiratory pump, and finally the forcing of respiration by means of increased content of carbon dioxide in the inspired air; but without apparent great success for any one of these methods. He proceeds:

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* As a matter of fact the history of lipaemia and fatty embolism begins with the experimental work of Magendie during the years 1821-36. The fact that Lower in 1669, and others later, made intravenous inejctions of large amounts of milk into dogs has sometimes been referred to as the beginning of the history of fat-embolism; but the tissue changes produced by such expermiental work were first noted in a gross way by Magendie.—Editor.

> *Page 135.*—"Save a few wounds of the abdomen, in which the blood-vessels or their nerves in that great vascular region were probably directly injured, there has been no case of shock except after shell-fractures of the thigh, and after multiple wounds through the subcutaneous fat. In this closure of the capillaries by fat-globules is known to take place. This is strong support for my discovery that shock may be produced in animals by injecting fat into the veins."
>
> *Page 150.*—"I found an electrical method useful against shock in animals, but I have not yet succeeded in adopting this method for use upon man.
>
> "In August, 1917, I sailed for my own country, bearing with me the certainty that fat embolism is a frequent, if not the most frequent, cause of shock as seen on the battle-field and the further certainty that the carbon-dioxide treatment is of advantage."

This is Porter's most complete statement of his work, although in the *Boston Medical and Surgical Journal, 1917, CLXXVI, page 248,* he makes a brief assertion, without evidence, that fat embolism is a cause of shock. He further states that "Fat in the blood stream is not injurious *per se;* its injurious effects are the product of fat embolism." See also *Comp. rend. Acad. d. Sc., 1917, 165, 164.*

It is very apparent from Porter's book and article that he has no knowledge of the pathology of traumatic lipaemia and fatty embolism beyond the obstruction of the capillaries, the engorgement of the veins and the resulting arterial anaemia—all three of which conditions may, or may not, give a clinical picture resembling the phenomena of so-called surgical shock, and are frequently mistaken for such as had been sufficiently emphasized by the present writer in the monograph in the International Clinics. Porter does not distinguish between pulmonary fat embolism and localized fat embolism of the brain, heart, kidneys, adrenals, etc., or a disseminated fat embolism, and apparently does not know that there are distinct symptom-complexes of fatty embolism. He apparently does not know that fatty embolism when it reaches such a degree as to become clinically manifest in symptoms resembling those of shock and collapse is chiefly a *cerebral fatty embolism* and not a *pulmonary* condition alone, and that minute cerebral lesions, haemorrhages, infarctions, etc., have already occurred that cannot be remedied by respiratory pumps, carbon dioxide respiration, electrical treatment, etc. Further, there is almost always an increase of temperature in fatty embolism and not a subnormal one as in shock. A knowledge of the pathology of the subject would have shown Porter that the treatment of fatty embolism is *preventive* and not *curative*.

The writer's article in the International Clinics was written in 1907 for the express purpose of showing surgeons the surgical frequency and mportance of fatty embolism, and the fact that it was usually mistaken for surgical shock and collapse, and that it had a specific pathologic and clinical entity of its own, with characteristic diagnostic signs—one of these, the presence of fat droplets in the sputum, was for the first time shown to be the earliest diagnostic sign of pulmonary fatty embolism. Without quoting too freely from this article a few particularly significant paragraphs are reproduced here:—

> *Page 3.*—"Fatal cases of fatty embolism from the common accidents of our large cities are every day diagnosed as "shock, coma, apoplexy, alcoholism, concussion, 'had heart', etc."
>
> *Page 4.*—"Without warning and without apparent cause (after fractures or amputations), a state of restlessness with mental anxiety, disturbance of heart and respiration, delirium and coma, sets in, and death may take place within twelve to twenty-four hours. In explanation and justification of these fatal cases, the surgeon frequently takes refuge behind a diagnosis of shock or concussion. It is extremely probable that the majority of these cases are the results of traumatic lipaemia and fatty embolism, and it is highly desirable that more attention be paid to the differential diagnosis of fatty embolism, shock, concussion, diabetic coma, lymphatic struma, alcoholism, etc."

Only one case out of thirteen of fatal fatty embolism autopsied by the writer had been correctly diagnosed clinically, and in this case, the diagnosis had been made by a laboratory assistant who had heard discussions of the condition in the pathological laboratory. "Shock, heart-failure, acute cardiac dilatation, cerebral haemorrhage, pneumonia, sepsis, insanity and alcoholism were the clinical diagnoses for the other cases, and the true cause of the symptoms remained unsuspected."

> *Page 19.*—"* * * deaths following fractures and amputations are probably often reported as the result of shock, 'heart-failure,' concussion, haemorrhage, pneumonia, sepsis, etc., when the real cause is fatty embolism. This has been the actual pathological experience of the writer, and must be true of medical practice in general."

In his review of the literature and in the descriptions of his own cases the writer has pointed out the varying symptomatology of fatty embolism, with the predominating low arterial pressure, venous congestion, symptoms of collapse, Cheyne—Stokes syndrome, etc., that so often give a clinical picture interpreted as shock. Series of animal experiments on hares, dogs and chickens were carried out showing the symptomatology and general pathology of fatty embolism in these animals to be similar to that in man. Synchronous tracings of carotid, auricular and jugular pressures were made, and frequently demonstrated to students in experimental pathology, showing the rapid fall of carotid pressure and steady increase of auricular and jugular pressures terminating in delirium cordis and death, as the result of the injection of oil directly into the jugular vein or heart.

Fatty embolism may be produced by all varieties of bone—injuries involving the fatty marrow, fractures, surgical operations, concussion, osteomyelitis, haemorrhages, presence of foreign-body, neoplasm, etc. By far the most common cause is fracture, and especially comminuted fractures; much less common is fatty embolism after injury to adipose tissue, bruises, wounds, burns, operations, childbirth, etc. Still more rarely is it associated with rupture of fatty liver, and lipaemia associated with poisons or diabetes as a cause of fatty embolism is very rare. The wounds of war causing fractures of large bones like the femur, tibia, etc., with the marked comminution and injury to the marrow associated with such wounds are *precisely the type of wounds with which we should expect fatty embolism to be associated. It undoubtedly is one of the most important surgical conditions of the present war.*

But is it shock? Both Bissell (*Surgery, Gynecology and Obstetrics, July, 1917, p. 8*) and *Porter* have utterly failed to see the point of the writer's monograph in the International Clinics. The object of that article was not to prove the identity of surgical shock and fatty embolism, but to show that surgeons most frequently mistake fatty embolism for shock, or something else, instead of making a correct diagnosis of the former condition. *Fatty embolism is a distinct clinical and pathological entity. It should not be mistaken for shock. Its occurrence should be anticipated in all injuries to bones containing fatty marrow. Its therapy will be preventive rather than curative.*

For a full discussion of the symptomatology and pathology of fatty embolism the reader is referred to the writer's monograph in *International Clinics, 1913,* D, *p. 171.*

Addendum. Since the above was written *Wiggers*: *Proceedings of Soc. for Exp. Biol. and Med. Soc., Dec. 19, 1917,* has published a brief note on Fat Emboli and Shock, in which he shows that the circulatory failure produced by fat emboli should be distinguished, for academic as well as for therapeutic reasons, from that due to surgical shock. His experimental work shows that neither the intravenous nor the intra-arterial injection of fat produces changes in the dynamics of the entire circulation comparable to those found in shock following exposure of the intestine. He, therefore, concludes that "the hypothesis that fatty emboli, either of the pulmonary or systematic vessels, is the cause of circulatory failure in surgical or traumatic shock is not corroborated by our experiments." This conclusion is, therefore, in harmony with my attempts to put fatty embolism on its own feet as a surgical entity distinct from shock.

As this proof is being read *Simond's* article in the *Jour. of Exper. Med., May 1, 1918,* has just come to hand. This contains another example of the gross mis-reading of articles, in that Simond says that Warthin, Bissell and Porter are convinced that fat embolism is "a cause" of surgical shock. As my article was written with a different view of the case, I fail to see how such a statement concerning it can in any way be obtained from it.

THE PERSISTENCE OF CRANIAL BONE ANLAGEN IN COMPLETE ACRANIA.*

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In monsters showing grossly a complete acrania, the tabular cranial bones may nevertheless be represented by rudimentary calcareous formations arising through a process of intra-membranous osteo-genesis. In a still born eighth-month foetus, showing craniorhachischisis, acrania, exencephalia and a correspondingly severe degree of agenesia, aplasia, hypoplasia and dysplasia in various portions of the central nervous system, the character and extent of such cranial bone rudiments have been studied in several hundred sections used for teaching purposes, and in every section such formations have been present. They occur as irregular, somewhat angular masses which are heavily impregnated with lime salts, as is shown by their intense blue-black staining with hemalum, and which vary in size from small granules up to masses nearly 100 microns in length. In association with such bone rudiments are to be found those structures which are concerned in the normal process of intramembranous osteogenesis; coarse fibre bundles; large angular connective tissue cells, the so-called bone corpuscles; and a ground substance which in the foetus shows marked staining reactions for connective tissue mucin. The lime salt deposit seems to occur in and upon the fiber bundles and is first noted as minute spherical bodies which mass together to form the characteristic angular structures.

In its finer detail, osteogenesis as found in this case of acrania is quite comparable to normal intramembranous ossification. It differs, however, in that no large bony masses are found. The calcareous spicules remain separated from each other, and scattered throughout the matrix without any formation of the radiating bars of bone found at the advancing border of the normal process. Nor is there evidence of inclusion of osteoblasts in the matrix to form bone lacunae. (See Figs. 1 and 2.)

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*From the Department of Pathology, University of Michigan, Ann Arbor, Mich.

Presented at the Meeting of the International Association of Medical Museums, New York, April 5th, 1917.

As might be expected from the marked developmental disturbance the distribution of the bone rudiments in acrania conforms but very roughly to anatomical relationships which might be considered as indicating areas of formation of particular cranial bones. It is more abundant however in the lateral portions of the area epithelio-serosa than beneath the area cerebro-vasculosa, and quite constantly is noted as occurring not just beneath the atypical integument but between a layer of nerve tissue and blood vessels externally and the hypoplastic brain tissue within.

The fact that intramembranous ossification has here proceeded but to a stage of detached spicules is interesting in view of the belief of many comparative anatomists that the intramembranous development of subcutaneous tabular bones is phylogenetically comparable to the formation of the integumental skeleton of certain lower vertebrates and that this in turn had as its precursor the formation of dentinous cutaneous spines.

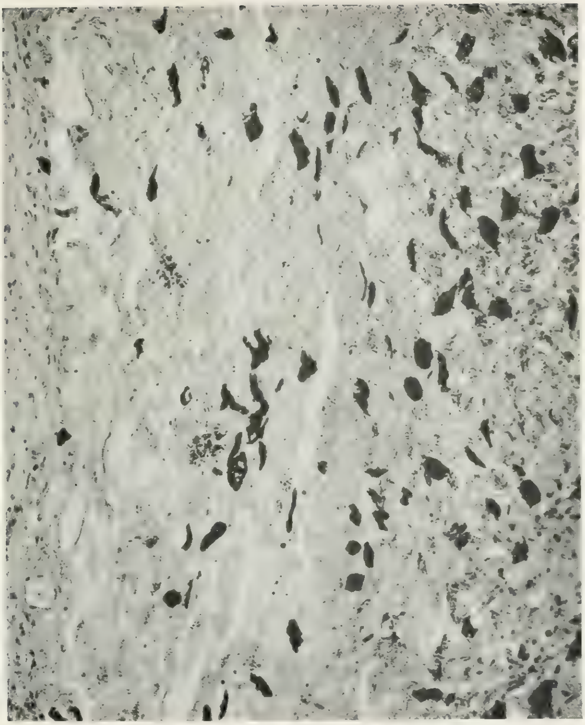

Fig. 1.—Microphotograph of Rudimentary Cranial Bone Anlagen in Case of Acrania. Spicules of Atypical Bone Formation Deeply Stained by Hemalum.

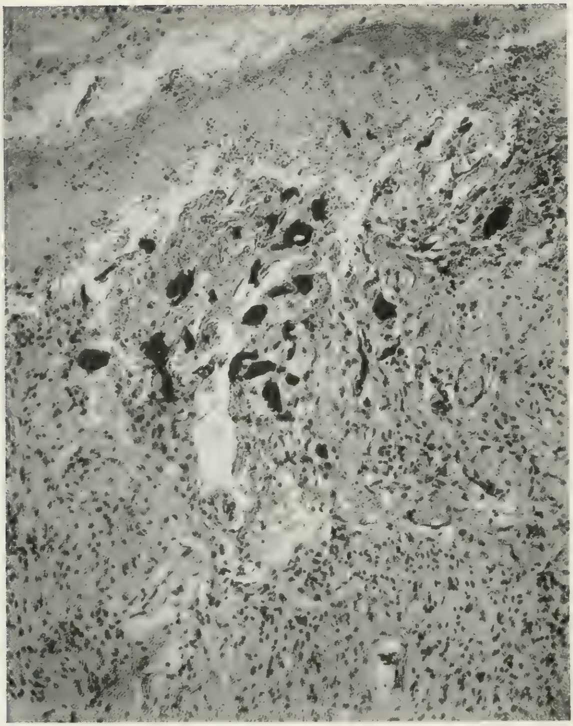

Fig. 2.—Microphotograph Showing Relationship of Rudimentary Cranial Bone Anlagen to Brain in Case of Acrania.

TOXIC JAUNDICE DUE TO DINITROPHENOL

A. S. Warthin
Ann Arbor

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May, 1918

A FATAL CASE OF TOXIC JAUNDICE CAUSED BY DINITROPHENOL.

A. S. Warthin.

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Ann Arbor, Michigan.

Poisoning by *dinitrophenol* is not mentioned by either Thompson or Oliver. Dr. Alice Hamilton, likewise, does not mention it in the Government Bulletin of occupational poisoning in munition workers. In a personal communication, however, she writes that she knows of no cases of dinitrophenol poisoning in this country, although she has suspected that some of the cases of picric acid poisoning reported were in reality dinitrophenol cases. Kober says that "Dinitrophenol may cause acute symptoms of industrial poisoning similar to those observed from nitrobenzol."

The physiologic and toxic action of the di nitrophenols (para-, ~~di-~~, meta- and ortho-) has been studied by Baumann and Herter, Hammerbacher, Gibbs and Hare, Röhl, Gibbs and Rechert, and Leymann. The fatal dose of dinitrophenol for a 1 Kg. dog was found to be 0.05.; when injected into the jugular vein the heart's action was markedly inhibited, the activity of the motor nervous system lowered and death occurred through respiratory or cardiac paralysis. Degenerative changes were found in liver and kidney, poikilocytosis without brown coloration of the red blood cells in the dog, and methemoglobin in the cat. These early pathologic studies are very incomplete and of little value. The experimental work was carried out chiefly from the physiologic side and little study made of gross or microscopic pathology.

There apparently exists in the literature only one observation of the pathological changes occurring in a fatal human case of dinitrophenol poisoning. (*Barral et Martin*: Intoxication par le dinitrophenol, Lyon Médical, Vol. 125, 1916, p. 276); at least, I have been unable to find any other. In the case reported the patient had been working for six months in a powder factory, engaged in the drying of dinitrophenol after its washing with water. When the turbines were active he was exposed to an atmosphere containing a fine spray mixed with particles of dinitrophenol. Until the day of his death he had not presented himself to the medical service. He was taken suddenly ill at mid-day, after leaving his work at the usual hour in the morning. The physician who examined him at the time found him suffering from intense headache, vomiting, bronchial rales, cardiac arrhythmia, pulse 110, temperature 40.8°. After a slight amelioration at thirteen hours, he died at fourteen and a half hours.

Autopsy showed the skin of the hands, feet, abdomen and forehead colored yellow; the hairs also were yellow. In the trachea and large bronchi there was a blood-tinged froth. The lungs showed a marked oedema; the other organs appeared normal. In the absence of any condition explaining the cause of the pulmonary oedema, the various organs and their contents were subjected to a toxicological examination. The urine contained albumin, aminonitrophenol and traces of dinitrophenol. No nitro-derivatives were found in the stomach. The bloody fluid and sputum obtained from the cut surface of the lungs showed a marked content in dinitrophenol. From the lungs and the blood of the heart there was obtained a notable quantity of dinitroenol. The liver contained aminonitrophenol without dinitrophenol. The reduction of dinitrophenol to aminonitrophenol appeared to be carried out chiefly in the liver. In the kidney a trace only of aminonitrophenol was found. The stomach contained no trace of nitro- derivatives.

Death was regarded as due to an *acute pulmonary oedema* due to the absorption by the lung of dinitrophenol. As the man was an alcoholic the specific action of the poison upon the lungs was thought to be favored by his alcoholism, the presence of alcohol favoring the dissolution of the dinitrophenol, and the alcoholic degeneration of the body retarding or preventing elimination of the poison.

The authors further state that as the result of experiments, as yet unpublished, upon the toxicity of dinitrophenol, the quantity of dinitrophenol found in the body of this case is not sufficient to explain his death on the grounds of a general intoxication.

They conclude that alcoholics and men presenting hepatic, pulmonary or renal lesions should not be employed in the handling of this product. On the other hand to prevent accidents that

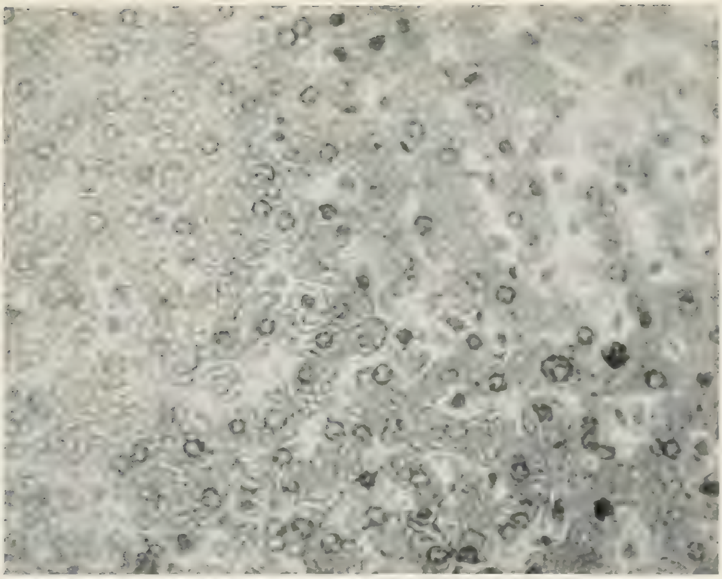

Fig. 1.—Border of Degenerated Area of Liver Lobule, Showing the Fatty Degenerative Infiltration and Simple Necrosis of the Liver Cells.

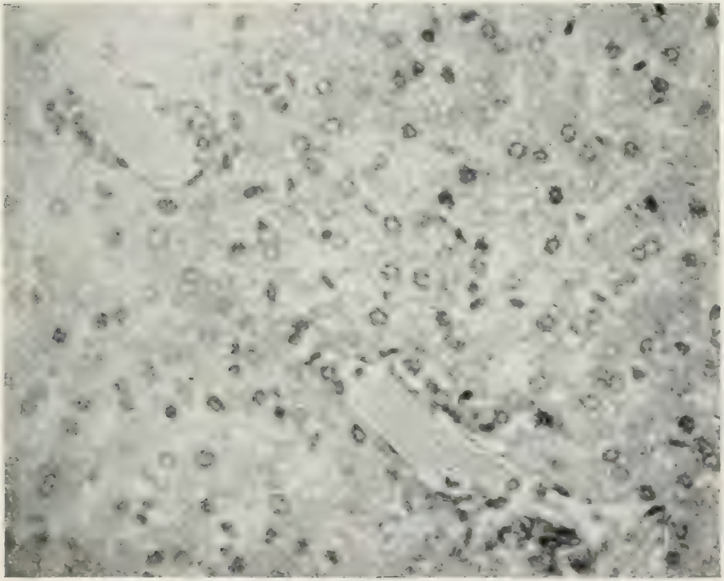

Fig. 2.—Agglutination Red Blood Cell Hyaline Thrombi in Central and Sub-lobular Veins in the Area of Fatty Degeneration and Necrosis of the Liver Lobule.

possibly might be fatal, the turbines should be covered while they are in use, and the workers should wear a mask during their manipulations.

In October, 1917, there was received at my laboratory a specimen of urine and liver from a man dying in a chemical plant where dinitrophenol was being manufactured. The man was said to have died "with all the symptoms of some kind of poisoning." No data concerning his symptoms in detail or the post-mortem findings were furnished us beyond the fact that he was jaundiced.

URINE EXAMINATION.

(*Dr. Weller.*)

Sample consists of 2 ounces of dark yellowish-red urine, slightly smoky, but with a definite greenish coloration.

Slightly turbid. Reaction faintly acid.

Albumin,—trace.

Bile pigment,—abundant. Foam bright yellow on shaking, Rosenbach's test for bile pigment, positive.

Microscopical examination of sediment obtained by centrifugation shows no crystalline elements. Very rich in epithelial cells, chiefly renal.

Tests for phenol derivatives, (both dinitro- and trinitro-) strongly positive. A portion of the urine was treated with bromine water. A precipitate was gradually thrown down. This was flocculent at first but later settled out as a heavy yellowish white solid (tribromphenol). Another portion was rendered strongly alkaline with NaOH when the color changed from light yellow to a deep orange red. These tests were duplicated upon normal urine to which a small amount of 5% phenol was added and then changed to nitrophenol by boiling with nitric acid.

PATHOLOGY OF LIVER.

Liver grass-green, icteric, capsule wrinkled, lobules smaller than normal to the naked eye.

Microscopically, the capsule is wrinkled, thrown into numerous folds, indicating very recent reduction in size. Lobules are smaller than normal. All blood vessels greatly congested, particularly central and sub-lobular veins. The central portions of the lobules are greenish, brownish or yellowish-stained from the acute icterus present, bilirubin in the liver-cells and bile capillaries. The liver cells in the central zone are disassociated, and show cloudy swelling, early necrosis, and fat droplets. Minute fat droplets (degenerative fatty infiltration)are present throughout the entire lobule, but are much more prominent in the intermediate and peripheral zones. (See Fig. 1.) These changes vary greatly in degree, being very much more marked in certain areas than in others. The blood vessels show an increased number of leukocytes and many of the periportal islands show a definite leukocyte infiltration. Hyaline and agglutination red cell thrombi are found in many of the intralobular capillaries. (See Fig. 2.) Brownish fragmented red cells occur also in the capillaries.

The microscopical appearances are those of a very acute degenerative hepatitis, the changes not differing from those seen in the liver as the result of many hepatotoxic poisons: chloroform, arsenic, TNT, phosphorus, etc., and in acute yellow atrophy and eclampsia. The only distinguishing feature, if there is one, is in the large number of hyaline thrombi present in this case. There appears to have been a very marked destruction of the blood cells. The urine shows a similar degenerative toxic action upon the kidneys, as revealed by the marked desquamation of tubular epithelium.

This case, while, unfortunately, incomplete in the absence of a thorough autopsy, shows evidence of a poison causing marked degeneration of liver and renal epithelium, acute degenerative hepatitis, with icterus, agglutination of red blood-cells, formation of hyaline thrombi, with the demonstration in the urine of nitrophenols.

Dinitrophenol must be added to the list of dangerous occupational hepatotoxic poisons, capable of producing acute yellow atrophy and toxic jaundice. At this time it is, therefore, increasingly important that suitable protection be provided for workers with this product in munitions manufacture.

THE ANN ARBOR

Some Practical Points in the Campaign Against Venereal Disease

A. S. Warthin
Ann Arbor

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May, 1918

SOME PRACTICAL POINTS IN THE CAMPAIGN AGAINST VENEREAL DISEASE

A. S. Warthin

Ann Arbor

The statistics of the incidence of venereal disease in the American Army, as shown by the chart given in Dr. Stokes' article,* are frequently quoted to show the favorable results obtained by the introduction of medical prophylaxis. Other factors, however, must be considered before the decline in the incidence of these diseases since 1909 can be ascribed entirely to the effects of prophylaxis. The withdrawal of the army from the tropics, its reduction in size, the small number of new recruits, and educational factors as well must be considered in the analysis of this diminished venereal incidence in the army between 1909 and 1915. As soon as the troops were again brought into service on the border with new recruits the incidence began to rise in 1913. The statement is frequently heard and also sometimes published that the experience of the American Navy with medical prophylaxis has been similarly successful in reducing the incidence of venereal disease in the Navy. As a matter of fact the statistics for the Navy, as shown by the charts published in Holcomb's article, show that since 1909, during the eight years in which medical prophylaxis has been carried out in the Navy, venereal infection has increased instead of diminishing. Under the system of medical prophylaxis the admission rate for gonorrhea has almost doubled, that for chancroid has more than doubled, while that for syphilis is but little higher. It is also very probable that the Navy statistics are more reliable than those from the army. See Tables 1, 2, and 3. There is, however, a still better way of estimating the effects of prophylaxis, and that is by considering the damage rate, as per Tables 4, 5 and 6. Table 4 for gonorrhoea shows that when prophylaxis went into effect in 1909 the damage rate per 10,000 increased to 16.6 and has not been lower than 15.05 since that time. The damage rate from gonorrhoea cannot, therefore, be said to show improvement under prophylaxis. As far as chancroid is concerned the damage rate for the four years preceding 1909 is lower than for any year since. Table 6 shows that the damage rate for syphilis since 1911 is somewhat lower than in preceding years. It is possible that the use of salvarsan may be responsible for this apparent improvement rate in the damage rate of syphilis. Taking it all in all the damage rate from venereal disease in the Navy has been raised rather than lowered.

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*Bull. of the Inter. Assoc. of Med. Museums, No. VII, 1918, p. 275.

Most significant are the efforts made in certain states, as California and Michigan, to attack the venereal problem from the standpoint of communicable diseases dangerous to the public health. A new epoch has been opened by the health measures placing the venereal diseases in the list of reportable diseases. The War has brought about what might otherwise have taken generations of effort.

That some of the citizens of the State of Michigan are awake to the significance of the situation is shown by two meetings held in Detroit last spring, at which the State Social Hygiene Association was revived, and by the called meeting held in Jackson in September. At this meeting a definite program was adopted. The following set of resolutions previously adopted by a similar meeting in California was unanimously adopted, and a permanent Committee appointed to go before the Governor with the request that a State Commission for the Control of Venereal Disease be appointed, and that active measures for the prevention of venereal infection at Camp Custer be carried out:

Program for the Prevention of Venereal Diseases in the State of Michigan.

1. Prostitution is to be suppressed vigorously and continuously, through the enforcement of the State laws, and the issuance of certificates of health to prostitutes for use in soliciting is not to be included in this program.

2. Prostitutes brought to the attention of the police or health authorities are to be examined; and all persons, male or female, capable of spreading venereal disease are to be isolated, under the provisions of the public health act, or local ordinance, and treated at public expense as long as there is danger in the opinion of the health officer, of their exposing others.

3. Under no circumstances are infected prostitutes to be "floated" into other communities, and if they are known to go from one community to another, the health officials of the places of destination are to be notified at once.

4. The State law requiring the report of syphilis and gonococcus infections by physicians', office numbers, is to be enforced to the letter, and in addition physicians are to be urged to obtain, and furnish to the local health officers, the names of the persons who are suspected of disseminating infection. The local health officers are, therefore, to investigate and supervise and isolate infectious cases according to the circumstances.

5. To provide and encourage the instruction of young men and women in the advantages of a clean life and the dangers from venereal disease.

6. To provide adequate opportunities for expert diagnosis, treatment, and advice for infected persons financially unable to secure proper attention for themselves, and to encourage the continuance of treatment until the patient is cured, or at least becomes non-infectious.

7. To provide free laboratory tests for syphilis and gonococcus infections for physicians, and encourage greater use of the tests for these diseases at the laboratory of the Bureau of Communicable Diseases of the State Board of Health.

The committee appointed at Jackson met the Governor and the War Board, and presented the situation to them. A committee of five was appointed by the Governor to make recommendations as to the method of proceeding with the preventive work. At a meeting of the committee of five held in Lansing the following recommendations were submitted:

1. The sources of infection to be located in every possible way.

By securing the co-operation of the military medical authorities in the reporting of cases from whom soldiers have acquired infection.

The appointment by the State Board of Health of a special medical inspector to be stationed at Battle Creek, and the detailing of inspectors to other points if necessary.

Co-operation with the local health authorities of various communities in the State.

Suggestions to the cities of Battle Creek and Kalamazoo of the desirability of securing the services of full-time Health Officers.

Furnishing, by the State, of free laboratory tests for venereal diseases.

2. Segregation of infected persons.

Infected soldiers to be segregated in camp, by military authority.

Infected women to be segregated in detention hospitals or by house quarantine, if necessary.

Hospital facilities at Detroit and Ann Arbor being now available, the Commission recommends the use of these hospitals until further arrangements can be made.

3. The treatment of infected persons.

Soldiers to be treated in camp by the military medical authorities.

Infected cases in the civil population to be cared for in the segregation hospitals above mentioned and in free clinics to be established at various points in the State.

4. The supervision of cured or arrested cases.

By paid social workers in each of the several communities near the encampment.

5. By enlargement of the protected zone.

The military authorities to be requested to extend the zones under authority of the Act of May 18, 1917.

6. By a campaign of education.

In the military camps, thorough co-operation with the Medical Corps of the army.

In communities throughout the State, under the auspices of the State Board of Health.

The above program, it is realized, is not complete. It offers, however, a definite step in the direction of lessening the terrible menace which is now confronting the nation and it further will give the State of Michigan the distinction of being a leader in this field of public health protection.

STATE BOARD OF HEALTH GIVEN SUPERVISION.

These recommendations were accepted by the Governor and the State Board of Health was directed to proceed with the preventive measures suggested. Co-operation of the State Board of Health with the military authorities at Camp Custer has already been secured and the machinery of the State Health Office has already been set in action along the lines outlined in the recommendations of the committee. Blanks for the reporting of gonorrhoea and syphilis have already been distributed, and the response from the physicians of the state is more encouraging than was anticipated. The blank used in reporting these diseases is shown here:

WAR MEASURE

PHYSICIAN'S REPORT OF A CASE OF GONORRHOEA OR SYPHILIS.

(This report must be mailed to the State Board of Health AS SOON as the physician has knowledge of a case of gonorrhoea or syphilis not to his knowledge previously reported.)

TO THE STATE BOARD OF HEALTH:

There has come to my knowledge a case of........................
(Gonorrhoea or Syphilis)
in the .... of ....
(Township, city or village) (Name of township, city or village)
County of ...., State of Michigan.
Name, initials or office number of the person infected..............
Age .... Sex .... Single ....
(Male or female)
Married .... Widowed ....

GONORRHOEA.

When contracted.......................Source of infection............
....
Is patient so guarded as not to be able to infect others..................

SYPHILIS.

When contracted.......................Source of infection............
....
Stage: Primary ( ), Secondary ( ), Tertiary ( ) Lesions present......
Is patient so guarded as not to be able to infect others..................
(Signed) .... M. D.
Date ....191.... Post Office..................

In many instances it will be a decided advantage to the public health if the physician will report not only the information asked for above, but a complete history of the case, and thus give opportunity to institute such restrictive measures as are indicated.

Complete and prompt reports of OPHTHALMIA NEONATORUM must be made.

The State Board of Health has placed a special Health Officer at Battle Creek for the protection of Camp Custer. Since November 18, 1917, this office has apprehended and placed under treatment the following number of venereal disease-carriers:

"44 women in the Hermann Kiefer Hospital, Detroit.
6 women in the Jackson Hospital.

12 women in the Devore Hospital, Grand Rapids.
2 women in Harper Hospital, Detroit.
5 women in their own homes.
20 men in the State Board of Health Hospital, Battle Creek.

January 26, 1918. W. F. English, Director."

For all cases placed in hospitals the State War Board is paying $15.00 per week, the total cost of board and treatment. In the local State Board of Health Hospital at Battle Creek the cost per patient is very much less.

As a final comment upon this question, the Great War will be well worth while if through it society is brought to realize the significance of the venereal diseases and to put them upon the basis of dangerous communicable diseases.

Warthin, A. S.: Bulletin "Public Health" of Michigan State Board of Health, Oct.-Nov., 1917.

VENEREAL DISEASES IN THE NAVY.

TABLE I.

GONORRHOEA.

YEAR	ADMISSION RATE PER CENTUM	YEAR	ADMISSION RATE PER CENTUM
1880	3.02	1899	2.48
1881	3.08	1900	2.20
1882	3.28	1900	2.29
1883	3.59	1902	2.46
1884	3.71	1903	2.77
1885	4.02	1904	3.72
1886	4.23	1905	5.04
1887	4.11	1906	6.20
1888	3.47	1907	4.90
1889	2.81	1908	5.69
1890	2.43	1909 Prophylaxis	10.25
1891	2.46	1910 begun	10.39
1892	2.79	1911	9.21
1893	2.51	1912	8.72
1894	4.00	1913	8.06
1895	2.50	1914	8.49
1896	2.13	1915	8.79
1897	2.05	1916	8.26
1898	2.09		

TABLE II.

CHANCROID.

YEAR	ADMISSION RATE PER CENTUM	YEAR		ADMISSION RATE PER CENTUM
1880	.76	1899		1.08
1881	1.21	1900		.90
1882	1.35	1901		.80
1883	1.32	1902		.90
1884	2.00	1903		1.06
1885	1.96	1904		1.33
1886	2.18	1905		1.30
1887	1.73	1906		1.72
1888	2.29	1907		1.19
1889	1.05	1908		1.25
1890	1.29	1909	Prophylaxis	2.75
1891	.86	1910	begun	3.37
1892	1.00	1911		3.14
1893	1.40	1912		3.50
1894	1.66	1913		2.81
1895	1.15	1914		4.33
1896	.92	1915		3.23
1897	.86	1916		3.50
1898	.91			

TABLE III.

SYPHILIS.

YEAR	ADMISSION RATE PER CENTUM	YEAR		ADMISSION RATE PER CENTUM
1880	5.39	1899		1.95
1881	4.90	1900		1.95
1882	5.86	1901		2.03
1883	4.60	1902		1.93
1884	4.00	1903		2.19
1885	3.68	1904		2.16
1886	3.90	1905		2.37
1887	3.25	1906		2.69
1888	3.85	1907		1.90
1889	3.66	1908		1.89
1890	3.07	1909	Prophylaxis	2.58
1891	2.45	1910	begun	2.25
1892	2.09	1911		2.71
1893	2.03	1912		2.30
1894	3.05	1913		2.19
1895	1.81	1914		1.98
1896	1.68	1915		2.13
1897	1.57	1916		2.22
1898	1.59			

TABLE IV.

DAMAGE RATE FOR GONORRHOEA (URETHRA).

YEAR	AVERAGE COMPLEMENT	ADMISSIONS	D.	DIS.	SICK DAYS	DAMAGE	DAMAGE PER 10,000
1880	10233	309	..	22	5932	27.20	26.5
1881	11118	343	..	3	5436	16.39	14.7
1882	10631	350	..	3	5279	15.96	15.01
1883	9874	354	..	3	5287	15.98	16.1
1884	10948	407	..	6	7507	23.50	21.4
1885	9191	370	..	4	5810	17.91	19.4
1886	9188	389	..	..	5618	15.39	16.7
1887	9618	396	..	..	4641	12.71	13.2
1888	9955	348	..	3	4109	12.72	12.6
1889	11219	316	..	1	5203	19.25	17.1
1890	11768	286	..	2	4665	13.87	11.7
1891	11501	284	..	3	5066	15.37	13.3
1892	11775	329	..	2	5080	14.87	11.7
1893	12109	304	..	3	4717	14.52	11.9
1894	12520	501	..	4	7103	21.45	17.1
1895	13191	330	..	..	6032	16.52	12.5
1896	14196	303	..	1	5210	14.73	10.3
1897	15734	323	..	2	6131	17.79	11.3
1898	23986	503	..	28	10735	43.40	18.1
1899	20819	517	..	9	11586	36.24	17.4
1900	23756	525	..	9	10794	33.99	14.3
1901	26873	617	..	2	10816	30.63	11.3
1902	31240	771	1	6	10360	31.88	10.2
1903	37248	1032	..	1	11643	32.39	8.6
1904	40555	1512	..	15	14953	48.35	11.8
1905	41313	2085	..	11	15137	46.96	11.3
1906	42529	2640	..	7	17958	52.69	12.3
1907	46336	2274	..	8	13912	42.11	9.08
1908	52913	3015	..	14	18229	56.80	10.7
1909	57172	5861	..	33	28801	95.40	16.6
1910	58340	6064	..	17	31836	95.72	16.4
1911	61399	5660	..	26	33867	105.80	17.2
1912	61897	5403	..	26	35140	109.00	17.6
1913	65926	5320	..	27	33204	104.46	15.8
1914	67141	5703	..	10	36218	104.22	15.5
1915	68075	5985	..	11	35404	102.49	15.05
1916	69294	5731	..	7	43357	121.96	17.6

TABLE V.

DAMAGE RATE FOR CHANCROID.

YEAR	AVERAGE COMPLEMENT	ADMISSIONS	D.	DIS.	SICK DAYS	DAMAGE	DAMAGE PER 10,000
1880	10235	78	..	2	1302	4.55	4.4
1881	11118	135	..	1	2602	7.62	6.8
1882	10631	144	..	2	2819	8.72	8.2
1883	9874	131	..	..	3051	8.35	8.3
1884	10948	219	..	1	4833	13.70	15.1
1885	9191	181	..	2	3614	10.90	11.8
1886	9188	201	..	5	4095	13.71	14.9
1887	9618	167	..	..	2878	7.88	8.1
1888	9955	228	..	..	2968	8.10	8.1
1889	11219	118	..	..	2714	7.43	6.6
1890	11768	152	..	..	3416	9.35	7.9
1891	11501	100	..	..	1939	5.31	4.6
1892	11775	118	..	..	2046	5.59	4.7
1893	12109	170	..	1	2913	8.47	6.9
1894	12520	208	..	1	3817	10.94	8.7
1895	13191	152	..	1	3401	9.81	7.4
1896	14196	131	..	..	3481	9.51	6.6
1897	15734	136	..	1	2754	8.04	5.1
1898	23986	219	..	5	5305	17.03	7.1
1899	20819	226	..	3	5747	17.24	8.2
1900	23756	214	..	1	5189	14.67	6.1
1901	26873	217	..	2	5592	16.31	6.0
1902	31240	284	..	..	5788	15.85	5.0
1903	37248	396	..	..	7644	20.94	5.6
1904	40555	542	..	4	7661	22.93	5.6
1905	41313	538	..	2	5469	15.98	3.8
1906	42529	733	..	..	6562	17.97	4.2
1907	46336	534	..	..	6311	17.29	3.7
1908	52913	665	..	..	6570	17.95	3.3
1909	57172	1573	..	1	9539	26.63	4.6
1910	58340	1968	..	1	9975	27.82	4.7
1911	61339	1929	..	..	12547	34.37	5.5
1912	61897	2169	..	..	12634	34.51	5.5
1913	65926	1855	..	..	11464	31.40	4.6
1914	67141	2908	..	1	14749	40.90	6.0
1915	68075	2200	..	..	10521	28.82	4.2
1916	69294	2436	..	1	12816	35.51	5.1

TABLE VI.

DAMAGE RATE FOR SYPHILIS.

YEAR	AVERAGE COMPLEMENT	ADMISSIONS	D.	DIS.	SICK DAYS	DAMAGE	DAMAGE PER 10,000
1880	10235	552	1	37	15527	61.42	60.0
1881	11118	545	1	18	14548	49.35	44.3
1882	10631	623	..	22	13898	49.07	46.1
1883	9874	454	1	28	11432	45.81	46.3
1884	10948	438	1	24	12817	47.51	43.3
1885	9191	339	..	19	8392	32.49	35.3
1886	9188	359	..	21	9530	36.60	39.8
1887	9618	313	..	11	8546	28.91	30.0
1888	9955	384	1	13	9416	32.72	32.8
1889	11219	411	1	18	12196	42.90	38.2
1890	11768	362	..	8	10095	31.65	26.8
1891	11501	282	..	19	9489	35.49	30.8
1892	11775	247	1	15	8629	31.57	26.8
1893	12109	246	1	14	7739	28.69	23.6
1894	12520	383	1	21	10635	40.13	32.0
1895	13191	239	..	13	11965	39.28	29.7
1896	14196	239	1	21	10239	38.95	27.4
1897	15734	248	1	29	11289	40.92	26.0
1898	23986	383	1	78	11720	71.60	29.8
1899	20819	406	2	45	15425	65.75	31.5
1900	23756	465	1	78	21791	99.03	41.6
1901	26873	546	2	73	21656	96.83	36.0
1902	31240	606	..	69	26794	107.89	34.5
1903	27248	816	..	132	34112	159.44	42.8
1904	40555	880	..	125	32389	150.98	37.2
1905	41313	981	5	92	39632	157.06	38.0
1906	42529	1147	..	91	41248	158.48	37.2
1907	46336	881	1	105	32656	140.62	30.3
1908	52913	1001	2	116	36645	159.11	30.0
1909	57172	1476	5	166	49647	221.49	38.7
1910	58340	1316	3	114	47971	189.92	32.5
1911	61399	1668	2	84	66660	225.62	36.7
1912	61897	1426	..	75	56841	192.80	31.1
1913	65926	1447	4	70	62630	208.58	31.6
1914	67141	1332	2	49	53016	170.72	25.4
1915	68075	1454	3	60	65682	211.45	31.6
1916	69294	1542	5	62	67814	218.78	31.5

THE ANN ARBOR

THE NEW PATHOLOGY OF SYPHILIS

Harvey Lecture
Academy of Medicine, New York
December 8, 1918

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THE NEW PATHOLOGY OF SYPHILIS*

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In an analysis of 4,880 autopsies performed at Bellevue Hospital during a period of ten years Symmers† found anatomic evidence of syphilis in only 314 cases, or 6.5 per cent. In a similar study made by myself of 750 autopsies at Ann Arbor during the last ten-year period evidence of syphilitic infection was found in 300 cases or in 40 per cent of the entire autopsy material. Nothing could better illustrate and emphasize the points which I hope to establish in this paper than the wide discrepancy between these two studies. This is made all the more striking when the character of the clinical material in the two hospitals is considered. In a great city hospital like Bellevue, in a great city like New York, with patients derived chiefly from the poorer classes, the incidence of syphilis would naturally be thought to be much greater than in a state hospital, like the university hospitals at Ann Arbor, in which the clinical material is drawn chiefly from the rural population of the state, representing the better elements of the middle class farmers, village storekeepers, mechanics and laborers. Is the latter rural population syphilized to a greater extent than the poorer working classes of New York? In 139 autopsies made at Ann Arbor in 1916-1917, fifty-six cases showed evidences of active syphilis, in

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†Journal of the American Medical Association, 1916, lxvi, 1457.

1915-1916 out of 79 autopsies there were 30 cases, and in 1914-1915 out of 58 autopsies there were 25 cases, and for the remaining years the incidence was 40 to 50 per cent annually. Does this mean a greater total incidence of syphilis in Michigan than in New York?

I believe that this striking difference in findings is chiefly dependent, not upon the clinical material, but upon the *different pathologic criteria employed in these two studies.* If we turn to Symmers' paper we find that the criteria employed by him were chiefly anatomic. His diagnoses were based upon the following lesions: Aortitis in 55.7 per cent of cases, aneurysm in 25.6, chronic interstitial orchitis in 39, lesions of the nervous system in 35.6, of the liver in 33.4, of the skin in 33.4, indurative atrophy of the base of the tongue in 25, osseous lesions in 14.9, of the respiratory tract in 10.5, of the lymph nodes in 6, and of the gastrointestinal tract in 2.2 per cent. It is very evident from Symmers' paper that many of the findings not classed as gummata were in reality gummatous processes and should have been classed as such. For example, hepar lobatum always means healed gummata of the liver. He takes no note of syphilis of the heart muscle, the pancreas or adrenals, or of the occurrence in the most varied tissues of small inflammatory infiltrations associated with the presence of the Spirochete pallida. In short his diagnoses have nothing to do with the spirochete and the most common lesions produced by this organism; but are based chiefly upon the gross pathologic anatomy of pre-spirochete days.

The pathologic anatomy of syphilis is still ruled by the dicta of the gross pathologic anatomists of the latter half of the last century. The statements in our textbooks concerning the pathology of this infection in its latter stages *are based almost without exception upon the occurrence of the gumma, and syphilis of an organ is said to be frequent or rare according to the frequency of gumma of that organ.* The gumma was practically the only anatomic lesion of syphilis recognizable by the early pathologic anatomists. Morgagni's knowledge of the gross pathology of syphilis (*lues venerea*) consisted almost wholly of observations upon gummatous lesions of the bones, aneurysm of the aorta, and changes in the lungs and kidney. He speaks particularly of never finding changes in the liver in bodies affected with the lues venerea. As it was not until the years 1831-1837 that syphilis was separated from gonorrhea and soft chancre by Ricord, there was no advance made in the pathology of syphilis in the first thirty years of the nineteenth century.

It is a very strange fact that Rokitansky, the father of modern gross pathologic anatomy, in the thirty thousand autopsies said to have been performed by him, should have added nothing to the knowledge of the pathology of syphilis. With a pathologic material drawn from a highly infected population his observations upon the gross pathologic anatomy of syphilis are amazingly few. Ulcers near the nails, necrosis and hyperostoses in bones, and inflammations of fibrous structures, and possibly gummata, constitute his apparent knowledge of this disease, as shown by his great work on gross pathologic anatomy. Virchow, likewise, in his *Cellular Pathology*, 1858-1860, barely mentions syphilis and, at that, not in connection with any essential pathologic feature of the disease. Nevertheless in 1858* he clearly distinguished the simple inflammatory (irritative) and the gummatous lesions of syphilis, and showed for the first time the part played by this disease in producing inflammatory conditions of the most varied organs and tissues. This article really laid the foundation for the modern knowledge of the pathology of syphilis obtained since the spirochete was discovered. But his separation of syphilitic lesions into the two types made little impression upon the syphilology of the next forty years. In Wagner's *Textbook of Pathology* (1862-1876), emphasis of the *syphiloma* (tuberculum s. gumma syphiliticum, tumor gummosus, gummy tumor) as the essential pathologic lesion of syphilis ruled completely the minds of both clinicians and pathologists up to nearly the close of the century, and still remains the chief part of the pathology of syphilis in our textbooks. This narrowing of the conception of the pathology of this disease was largely due to the very valuable and comprehensive article by Baümler on syphilis in the von Ziemssen's Handbook (1874). The chapter on the general pathologic anatomy of syphilis in this article concerns itself chiefly with Wagner's conception of the syphiloma; Baümler's monograph has been the fount of inspiration for the majority of textbook articles on syphilis written since 1875.

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*Ueber die Natur der constitutionell-syphilitischen Affectionen, Arch. f. Path. Anat. u. Phys., xv, 217.

As the relationship of tabes and paresis to syphilis became more evident during the next two decades the conception of "postsyphilitic," "metasyphilitic," and "parasyphilitic" processes arose in explanation of this relationship. Fournier (*Les affections parasyphilitiques*, Paris, 1894) was chiefly responsible for the use of this term and for the view that a large number of pathologic conditions bore a definite relationship to syphilis, but were not syphilis and were not necessarily caused by it. Paresis, tabes, aortic aneurysm, arteriosclerosis, a variety of conditions of the nervous system, leucoderma, leucoplakia, and many other affections were regarded as parasyphilitic affections. The association of a typical form of aortitis with aneurysm, paresis, tabes, and other parasyphilitic conditions gradually led to an acceptance of its syphilitic origin and nature. Nevertheless, up to the discovery in 1903 of the Spirochete pallida, the gumma remained the one specific histopathologic lesion of syphilis.

With the discovery of the etiologic agent of syphilis it was to be expected that a change would be wrought in our concepts of the pathology of the disease, and that expectation was soon fulfilled. Parasyphilis has disappeared as the various parasyphilitic affections have been shown to be active syphilis with living spirochetes still present in the affected tissues. The term is now a misnomer. To the pathologic criteria of the disease there have been definitely added during the last decade the characteristic lesions of the central nervous system and syphilitic mesaortitis. The Harvey lecture by Fordyce in 1915 on "Some Problems in the Pathology of Syphilis" expresses very fully the generally accepted knowledge of the pathology of syphilis of the present day. He recognizes that "in all stages and in all organs the lesion begins in the perivascular lymph spaces as a lymphocytic and plasma-cell infiltration;" but he still says that "the type of lesion of the tertiary period is the gumma." He advances the pathology of syphilis only by the full recognition of the syphilitic nature of the nervous lesions and mesaortitis. Of the pathology of latent syphilis in other organs and tissues he has this to say: "Aside from gummatous involvement of the viscera, little is known of the effects of the infection on the various organs." My investigations and their results begin here in the demonstration that the gumma is not the type of lesion of late or latent syphilis, and that the viscera are involved in all cases of latent syphilis, not by gummatous processes, but by specific inflammatory processes, eventually fibrosis, usually mild in character, but acquiring pathologic importance because of their progressive character.

As soon as the Levaditi method of demonstrating the Spirochete pallida in sections was published, I began investigations as to its occurrence and distribution in the tissues, and my attention was first drawn to congenital syphilis because of the greater ease of demonstrating the spirochetes in the tissues of such cases. As a result of such studies important facts concerning the incidence of Spirochete pallida in the heart muscle of congenital syphilitics have been added to our knowledge, as, for example, the constant presence of spirochetes in the hearts of cases of congenital syphilis dying before or at birth, the occurrence of focal fatty changes in the myocardium due to the colonization of the organism, and of a specific type of interstitial myocarditis due to the same cause. The essential lesion in congenital syphilitic myocarditis was shown to be edema of the interstitial tissues, often giving reactions for mucin, infiltration with lymphocytes and plasma cells, and fibroblastic and angioblastic proliferations. Spirochetes were found to be constantly present in such lesions, often in enormous numbers. That spirochetes could be present in great numbers in the tissues of congenital syphilis without producing tissue changes was also shown.

From the study of the lesions of congenital syphilis it was a natural step to that of the pathology of acquired syphilis. Similar lymphocyte and plasma-cell infiltrations associated with spirochete localization were found in the tissues and organs of known cases of acquired syphilis, aortic aneurysm, tabes, paresis, etc., but it was not possible to demonstrate the presence of spirochetes so readily or in such a large proportion of cases, owing to their smaller numbers and widely scattered distribution. Nevertheless, the demonstration of the organism was successful in such a large number of cases (75), as to make the specific syphilitic nature of these lesions certain. In the progress of these studies the specific inflammatory lesions of spirochete localization have been found in the myo-, endo-, and pericardium, the aorta, pulmonary and other large arteries, nervous system, liver, pancreas, adrenals, testis, prostate, prevertebral and mesenteric tissues. These lesions vary greatly in size, from minute collections of few cells to larger infiltrations just visible to the naked eye. Every stage of development, from the early active lesions to complete healing and fibrosis was observed; but no cases were found in which there were no active lesions. Complete healing throughout the body was never observed. The marked tendency of the lesions to undergo fibrosis and healing with the formation of dense hyaline scar tissue was a striking feature and regarded as evidence of the relatively avirulent character of the organisms. Spirochetes may be found in all stages up to nearly complete healing, but were never found in the dense fibroid areas. A detailed description of these lesions of latent syphilis will now be given.

THE MICROSCOPIC PATHOLOGY OF LATENT SYPHILIS

Nervous System.—The central nervous system was examined in only a small percentage of the material, the head much more frequently being opened at autopsy than the spinal column. No especial study was made of either brain or cord, and the changes noted in these were only those found in the ordinary routine of microscopic examination accorded all tissues and organs obtained at autopsy. The most constant changes were those found in the *meninges.* In practically every case of latent or clinical syphilis autopsied some degree of thickening of the meninges was noted. The dura was constantly more adherent and thickened. No active syphilitic foci were however, ever found in this membrane. Focal thickenings of the leptomeninges were found in practically every case. These varied in all possible degrees. They were most common over the parietal convolutions, and along the median surfaces, being most easily seen over the sulci. They more frequently involved the arachnoid than the pia; but the focal thickenings very frequently represented fibroid areas involving both pia and arachnoid. Thickening of the wall and more or less obliteration of the meningeal vessels were usually found associated with the localized fibrosis. In the great majority of the brains examined these meningeal focal thickenings were small, usually pinhead in size, and sharply circumscribed. Only in clinical cases of paresis, tabes, cerebral syphilis, cerebral gumma and "toxic psychosis" were they larger, more diffuse and more marked. Transition stages from these small focal lesions to the larger ones were found. The great majority of these focal fibroses of the leptomeninges were healed inactive areas, plasma-cell infiltrations and fibroblastic infiltrations being found only in the more active cases of syphilis. They appear in the latent cases to represent old and early lesions in the history of the individual infection. The occurrence of active lymphocyte and plasma-cell infiltrations in the meninges in old latent cases of syphilis seemed, however, to parallel the degree of activity of the lesions found in the heart, aorta and other tissues. Precisely the same lesions in the meninges occurred in the nonparetic and nontabetic cases of syphilis as in those showing a clinical paresis or tabes, the only difference being one of degree. Active meningeal lesions have been found more frequently in young adults with congenital syphilis than in the old cases. Similar lesions occur in the meninges of the cord; and, as in the case of the cerebral meninges, the degree of these meningeal changes usually corresponded to the severity of the lesions in other organs and tissues. The meninges of the cord usually showed the most marked changes in cases of tabes and paresis, but a few exceptions to this were found in latent cases. The meningeal changes noted by me associated with syphilis, both latent and clinical, correspond in general with those described by LeCount and other writers as characteristic of meningeal syphilis. The focal chronic leptomeningitis regarded by some writers as the result of chronic alcoholism, would appear from my experience to be the result of syphilitic infection rather than of alcoholism. It is true, that some of my most marked cases of meningeal fibrosis were both alcoholic and syphilitic; but precisely the same meningeal changes occur in those cases without a history of alcoholism.

Focal infiltrations of lymphocytes and plasma cells were found in both *brain* and *cord* in cases not regarded clinically as paresis or tabes. These infiltrations were perivascular and were sometimes associated with proliferative changes in the vessel, at other times not. The character of these minute scattered lesions is precisely identical with those found in the brain and cord, in paresis and tabes, the differences being only those of number and degree. In two cases diagnosed clinically as "toxic psychosis" these lesions in the brain were so numerous as to suggest a pathologic diagnosis of early paresis. Two other cases without nervous symptoms gave similar microscopic findings. In one case of secondary syphilis dying from salvarsan poisoning the brain showed scattered perivascular plasma-cell infiltrations.

The question is raised by these findings as to their frequency in syphilis and their relation to the symptoms of paresis and tabes. Is every case of syphilis, to a slight degree, at least, a paretic or tabetic? There can be no doubt that pathologically there are borderland cases just as there are clinically such; and my experience would lead me to believe that probably every case of old syphilis will present in the brain and cord the same scattered perivascular infiltrations of lymphocytes and plasma cells found in all other organs and tissues. Such infiltrations represent simply the local reaction to the presence of spirochetes; and their relation to paresis and tabes may be simply one of degree, with reference to the number of infecting organisms, the degree of intoxication produced, and the resulting destruction of nerve tissue and functional disturbance produced.

Minute infiltrations of lymphocytes and plasma cells are of frequent occurrence in and about the *spinal ganglia*, the *spinal nerves* and the large *peripheral nerves*. No spirochete studies have been made of these, and their syphilitic etiology is assumed because of their identity with known syphilitic lesions in other organs and tissues, and their constant association with such.

Similar infiltrations are also very common in and about the *sympathetic nerves* and *ganglia*, particularly in the solar plexus and periadrenal plexus. Fibrosis, atrophy, and pigmentation of these ganglia have been observed in connection with such infiltrations. In three cases of Addison's disease due to syphilitic fibrosis and atrophy of the adrenals, the adrenal and solar plexus showed especially marked syphilitic infiltrations.

The tendency of the nervous system to spirochete localization

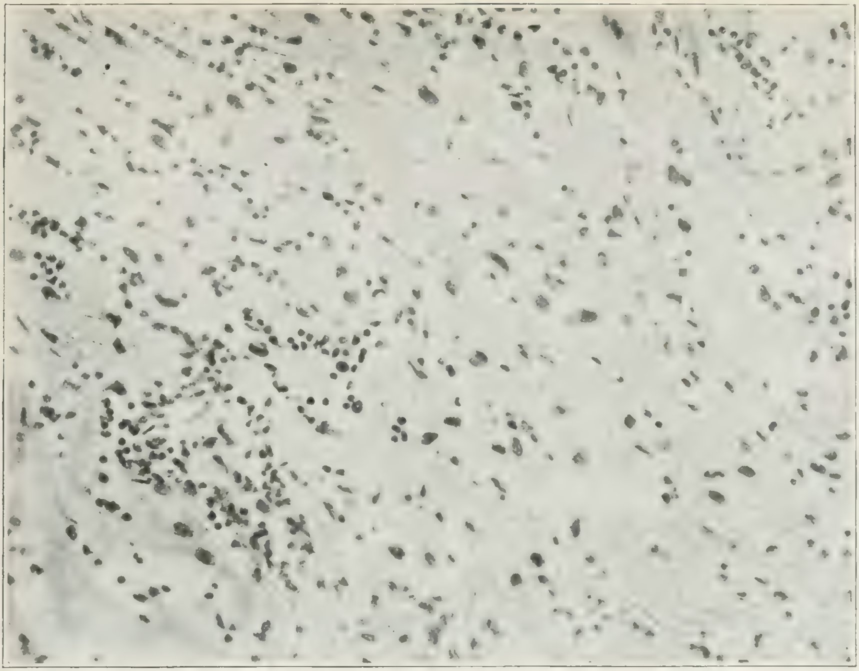

Fig. 1.—Chronic syphilitic myocarditis. Unsuspected latent syphilis. Sudden death. Male, aged 52 years. Dilatation of left ventricle. Wall of ventricle showed diffuse plasma-cell infiltrations. Spirochetes present throughout these infiltrations.

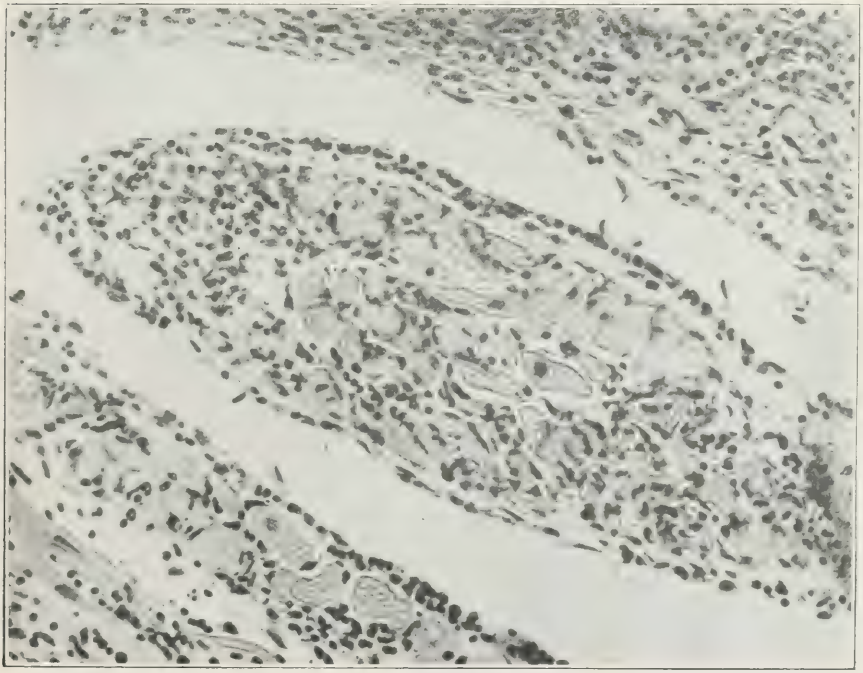

Fig. 2.—Chronic syphilitic myocarditis. Male 45 years of age; sudden death. Syphilis not suspected by clinicians; aneurysmal dilatation of left ventricle at apex. Diffuse plasma-cell infiltration of papillary muscles and wall of left ventricle at apex. Spirochetes present.

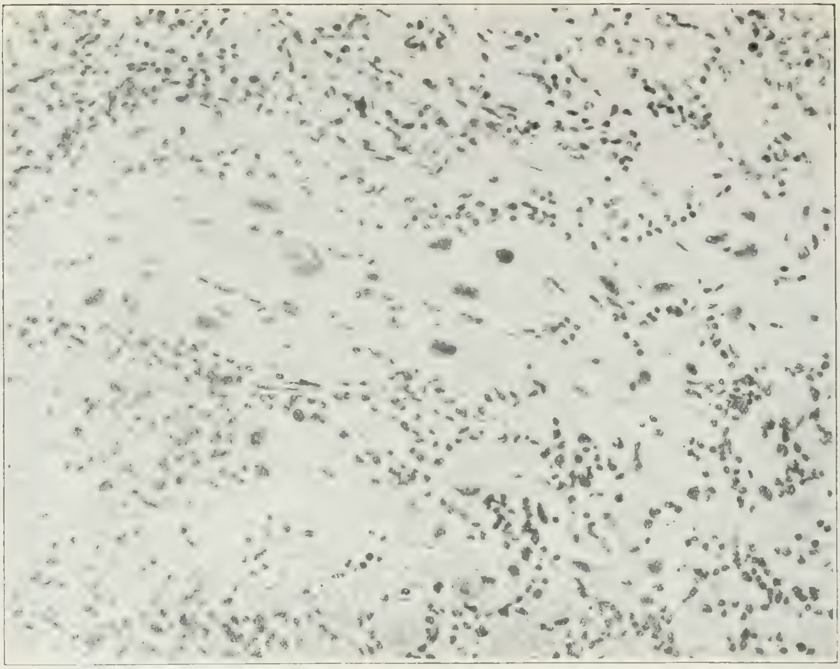

Fig. 3.—Chronic syphilitic myocarditis. Unsuspected latent syphilis in middle-aged man, sudden death More severe process than in preceding. More marked plasma-cell infiltrations of left ventricle wall above apex. Spirochetes.

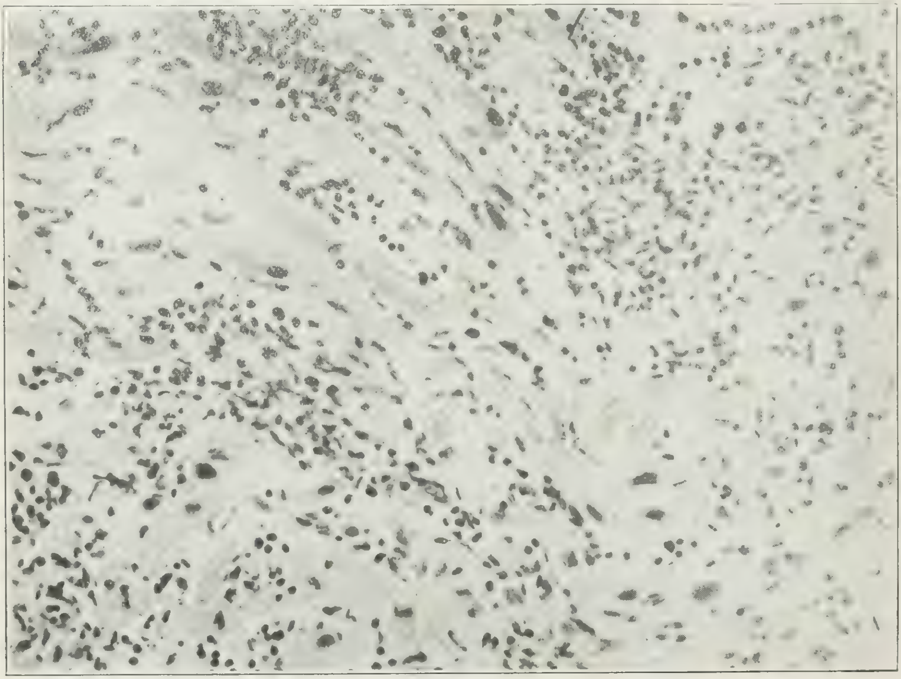

Fig. 4.—Chronic syphilitic myocarditis. Sudden death in middle-aged male with history of "cured" syphilis. More active process; plasma-cell infiltrations more diffuse with larger focal infiltrations approaching miliary gummata. Abundant spirochetes.

and to focal reactions of lymphocyte and plasma-cell infiltrations would appear from our material to be less than that of the heart, aorta, and other tissues, but this impression may be due entirely to the smaller number of cases in which the central nervous system was examined, and to the more superficial study accorded it. The routine examinations reveal, at least one very important fact that such minute lesions as occur in other organs in syphilis are found also in the nervous system when no clinical symptoms of its involvement are present.

Heart.—The heart in every case showed microscopic lesions characteristic of spirochete localization; and in this organ more frequently than in any other has the spirochete itself been demonstrated by the Levaditi method. The cardiac lesions in the cases in which syphilitic infection was known to exist, and in those in which it was not suspected are identical. They vary greatly in degree. To the naked eye the hearts of the cases included in this autopsy material showed as a rule dilatation, hypertrophy, atrophy, and fibroid patches in the wall of the left ventricle. In many cases no fibroid changes were visible to the naked eye, and the occurrence of fibrosis and active infiltrations was determined only by the microscopic examination. The portion of the heart most frequently involved was the anterior wall of the left ventricle near the apex, the adjacent portion of the septum and the posterior left ventricular wall near the mitral ring. In cases of congenital infection the right ventricular wall may be chiefly affected. It must be emphasized that the determination of cardiac syphilis is essentially microscopic; when no myocardial changes can be seen by the eye the microscopic examination may reveal the most extensive lesions. This is especially true of the more acute and active cases.

The essential lesion of cardiac syphilis is an interstitial myocarditis characterized by infiltrations of lymphocytes and plasma cells along the vessels between the muscle fibers. These infiltrations are usually patchy or diffuse, very rarely focal or circumscribed, thus differing from streptococcus myocarditis. The infiltrations vary in degree, but usually are slight, the cells often being arranged in close single file between the fibers. To a superficial glance there appears to be only a slight increase of the interstitial nuclei. Polynuclears are few in the infiltrations, and eosinophiles are not present. The cells of the infiltrations are probably chiefly histogenetic lymphocytes and young formative cells. Large epithelioid fibroblasts are very common, especially in the older, healing areas. Giant cells are rare. (See Figs. 1, 2 and 3.)

The entire heart wall from epicardium to endocardium, including the papillary muscles, may be involved in the infiltrations; but in the average case they lie nearer to the endocardium, often just beneath it, or in the middle layer of the myocardium. In acquired syphilis they rarely begin on the epicardial side, as they frequently do in congenital syphilis. In the most severe cases larger areas of infiltrations are grouped around the coronary arterioles. These may reach such a size as to suggest miliary gummata (see Fig. 4). Caseation, however, does not occur in these larger infiltrations. In two cases only were true gummata found in the myocardium. These were associated with the diffuse plasma-cell infiltrations.

In the more acute, severe and active cases the stroma of the infiltrated areas in the myocardium is edematous, often giving a slight reaction for mucin with specific dyes. In the older healed areas the stroma becomes fibroid and hyaline. In the great majority of cases the myocardium shows healed, fibroid areas in association with the active infiltrations (Figs. 5 to 8). In many cases the fibroid areas predominate, and search may be necessary to show the presence of active infiltrations. This is true especially of the older unrecognized cases. In every case, however, such active areas have been found, and no completely healed cases have been seen. A progressive fibrosis of the myocardium always takes place. In acquired syphilis the fibroid areas are always larger on the endocardial side; but in some cases they have extended completely through the myocardium. When this is the case, both endocardium and pericardium are thickened, and the latter usually shows a localized adhesion. These marked changes practically always occur just above the apex, in the anterior wall of the left ventricle; aneurysmal dilatation of the weakened wall at this point is not uncommon; rupture of the wall may take place as in two of our cases. More frequently, however, thrombosis occurs on the thickened endocardium overlying the fibroid patch, and death usually results from the progressive thrombosis of the left ventricle, or from embolism. In thirty of our cases thrombosis of the left ventricle over an area of syphi-

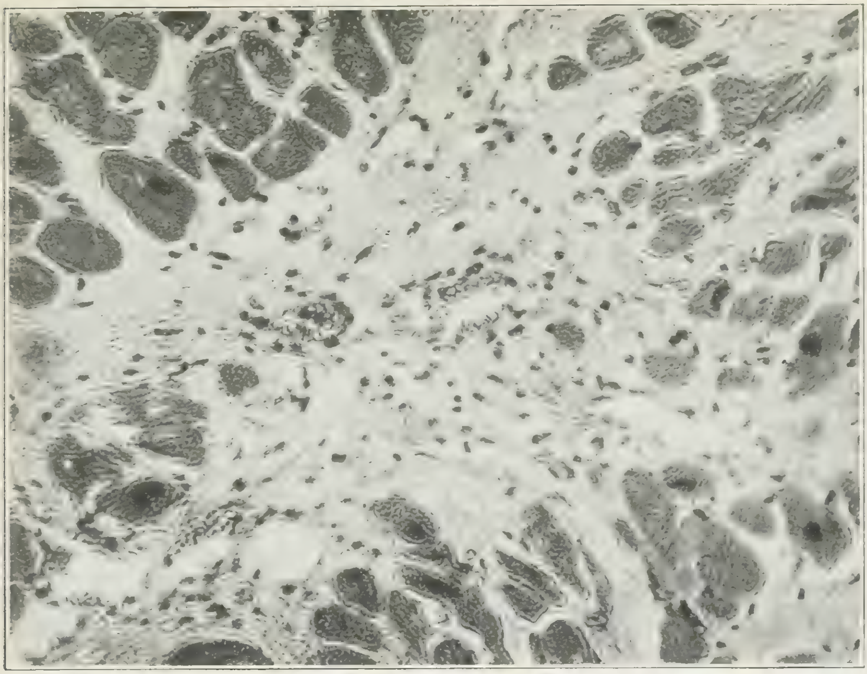

Fig. 5.—Chronic syphilitic myocarditis. Older process. Fibroid heart. Case of diabetes; unsuspected latent syphilis. Small active area in left ventricle wall in healing stage. Few spirochetes.

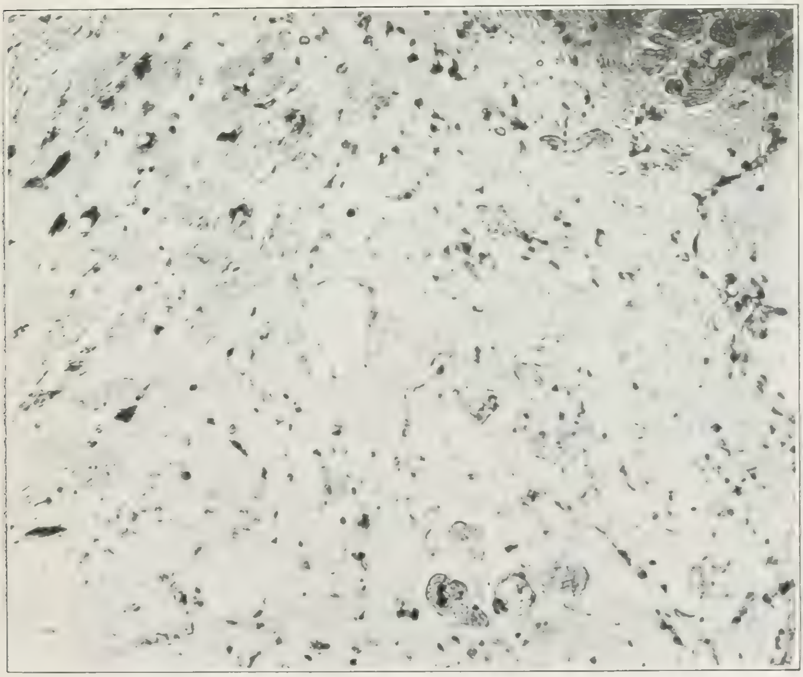

Fig. 6.—Chronic syphilitic myocarditis. Left ventricle wall from case of syphilis contracted 14 years previously. Suicide. Fibroid areas in heart with active plasma-cell infiltrations. Few spirochetes.

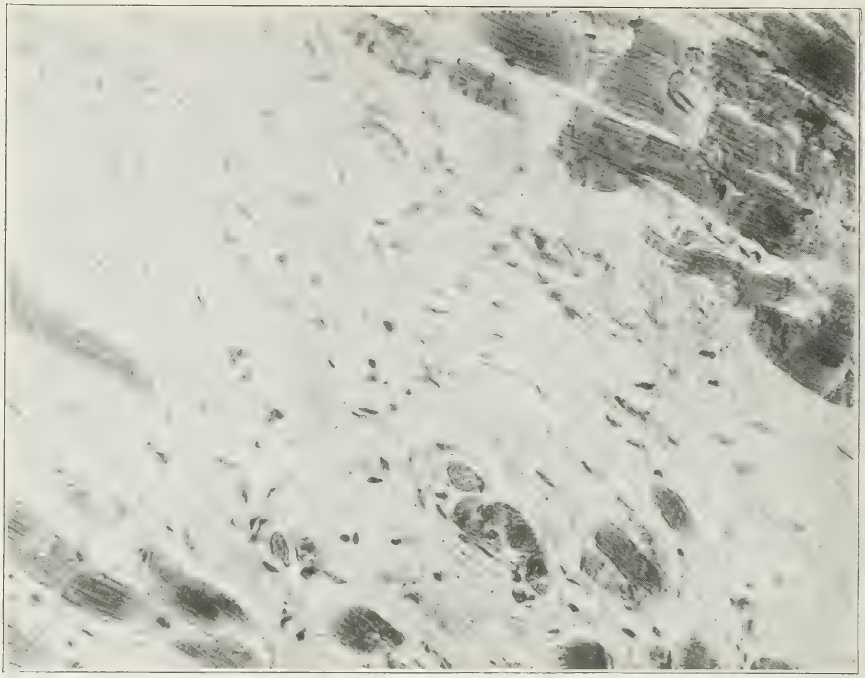

Fig. 7.—Chronic syphilitic myocarditis. Old "cured syphilis;" negative Wassermann; cardio-vascular-renal symptom-complex; dilated, fibroid heart. In areas showing no more active plasma-cell infiltration than in photograph spirochetes found in small colonies.

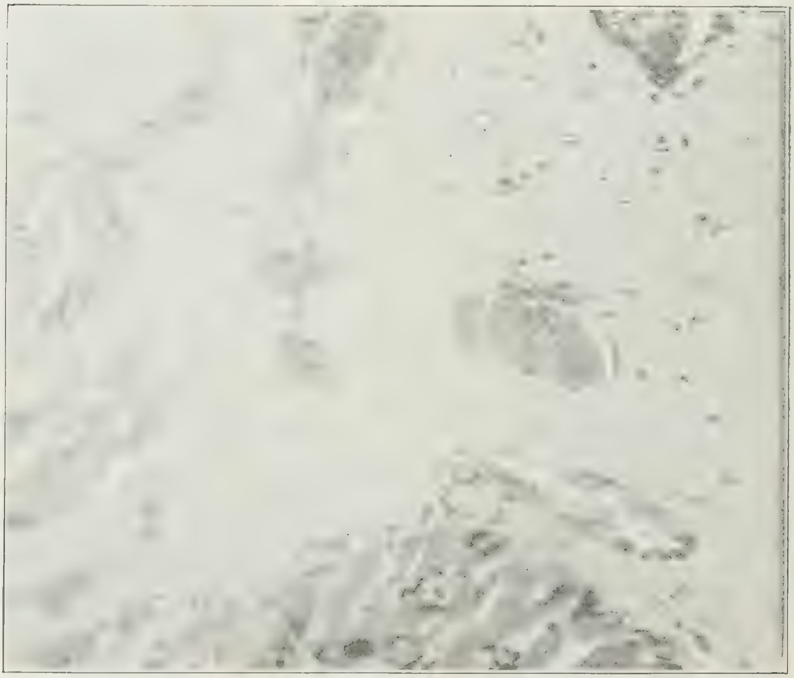

Fig. 8.—Chronic syphilitic myocarditis. Nearly healed fibroid area in left ventricle wall of old "cured syphilis." Slight plasma-cell infiltrations. Few spirochetes found after prolonged search.

litic infiltration or fibrosis of the ventricular wall was the cause of death. In the great majority of the cases of latent syphilis the left ventricle was dilated, and such dilatation was either the chief or an accessory cause of death. The "fibroid" heart is the ultimate outcome of all cases of latent syphilis. (See Figs. 7 to 11.)

In the congenital and active acquired cases spirochetes are fairly easily demonstrated between the heart muscle fibers. In the older cases, with fibrosis more or less well advanced, the demonstration of the spirochete becomes a task requiring patience and determination, spread often over days or weeks. They are, nevertheless, more easily found in the heart than in any other organ or tissue, so far as our experience goes. (See Figs. 12 to 15.)

The parietal and mitral endocardium appears resistant to the spirochete to a much greater degree than that of the aortic valves. In no case have I been able to demonstrate the occurrence of syphilitic changes in the mitral valves. Secondary streptococcus or staphylococcus endocarditis with mitral stenosis or insufficiency was in a number of cases, particularly those of congenital syphilis, the immediate cause of death. The heart of congenital syphilis seems to give a local predisposition to secondary infections. Sclerosis of the coronaries may or may not be associated with syphilitic myocarditis. In my material marked coronary sclerosis was rather a rare finding; the coronary involvement was perivascular rather than primarily vascular. Even in a number of the angina pectoris cases the coronary sclerosis, as far as the larger branches were concerned, was not marked, although these cases all showed marked fibrosis of the myocardium. Thrombosis of the coronaries was not observed in any case. The smaller terminal arterioles and capillaries are obliterated and destroyed by the perivascular infiltrations and proliferations, while the larger coronary branches rarely show much sclerosis, except in the cases showing a general arteriosclerosis. A striking feature of the fibroid areas is the dilatation of preexisting capillaries or veins or a new formation of such in the fibroid areas. Often such areas appear cavernous or sinusoidal, because of the large blood spaces present having practically no wall but that of the lining endothelium. These appearances are probably the result of a compensating circulation in newly formed capillaries. In younger scars the new formation of capillaries is very striking, and this vascular proliferation appears to be one of the distinct features of syphilitic myocarditis.

The heart muscle itself in all of the cases presented varying degrees of hypertrophy with simple and brown atrophy, fatty degeneration, and necrosis, all of these changes usually being present in the same heart. In the immediate neighborhood or periphery of the infiltrations the heart muscle fibers often showed no changes at all; in other cases fibers extending through the lesions showed only hypertrophy. I have previously shown that colonies of spirochetes may be found in heart muscle appearing perfectly normal. While this is most common in cases of congenital syphilis, it is also found in late acquired syphilis. It is evident that the toxic action of such spirochetes upon the muscle fibers must be very slight indeed. The intensive study of these cardiac lesions tends to emphasize more and more the mild and slowly progressive nature of the latent syphilitic infection.

The clinical features of these heart lesions can not be presented in detail here, and for the present only generalizations can be given. While a history of symptoms is wanting in some cases, the great majority of the cases included in this material presented symptoms of cardiac weakness, and circulatory disturbances. A very large number of the cases were frankly those presenting the cardio-vascular-renal complex. The termination of the case was frequently cardiac dilatation. Shortness of breath, palpitation, precardial pains, anginal attacks, irregularity of pulse, swelling of ankles, dizziness, general weakness, ringing in ears, etc., were the most common subjective symptoms. All of our cases of angina pectoris were syphilitic. The blood pressure may be high or low; the cases are about evenly divided in this respect. The disturbances of rhythm are very prominent and of every variety; the most interesting cases studied in the Clinic of Internal Medicine coming to autopsy belong to this material. "Functional" murmurs were common. The final clinical picture in all was that of an insufficient heart—a heart that could not do its work properly. The majority died a cardiac death; as shown by the hypertrophy and dilatation of the heart, and the chronic passive congestion of lungs and other organs. The chief pathologic findings at autopsy were those of a myocardial insufficiency ("fibroid heart") without (in the great majority of cases) accompanying valvular lesions.

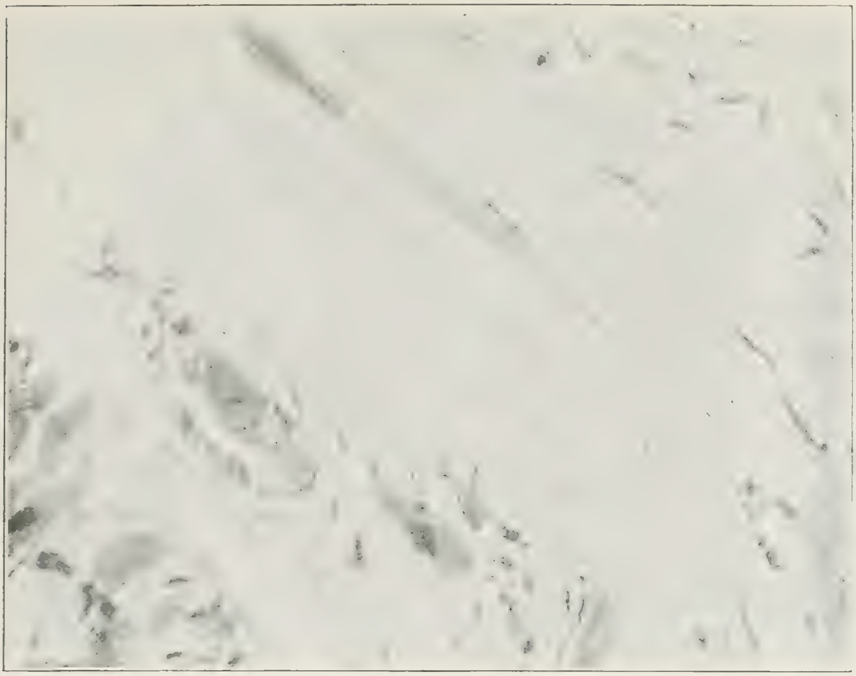

Fig. 9.—Chronic syphilitic myocarditis. Completely healed fibroid area. In such hyaline connective tissue without plasma-cell infiltration spirochetes have never been found.

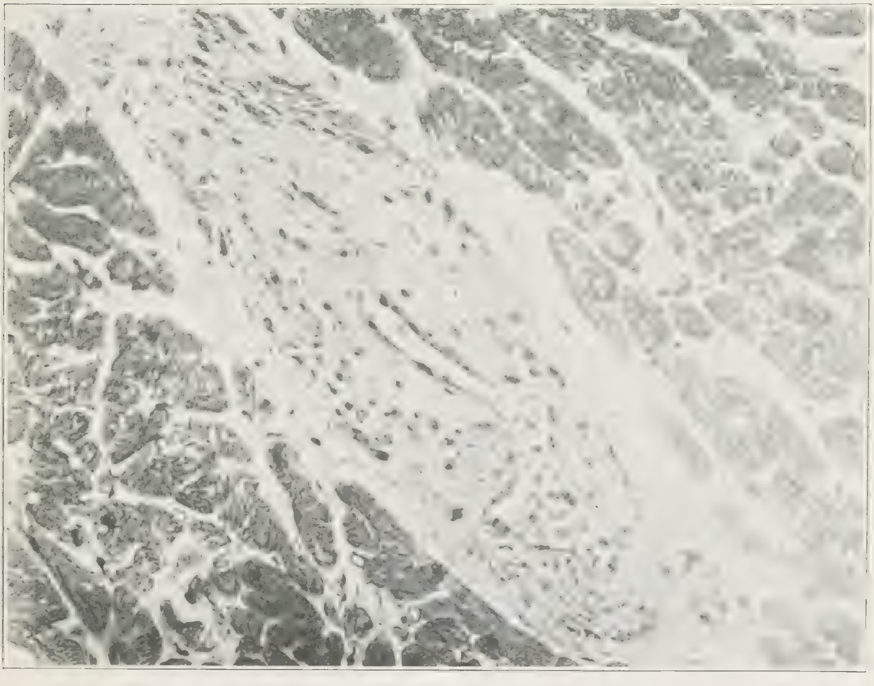

Fig. 10.—Tangential section of coronary vessel showing slight active syphilitic infiltration.

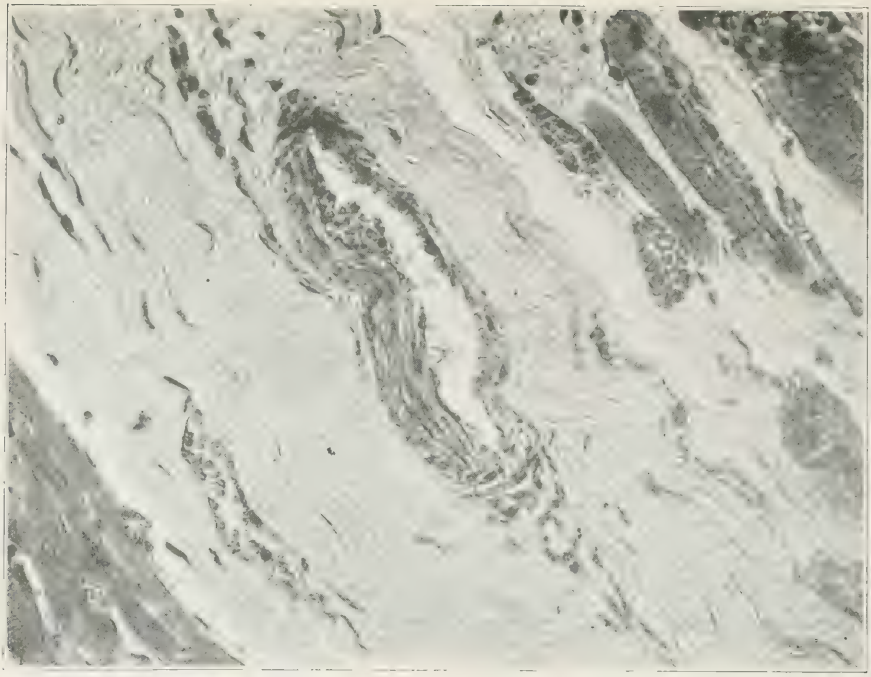

Fig. 11.—Similar section, from same case, showing complete healing; fibrosis without plasma cells.

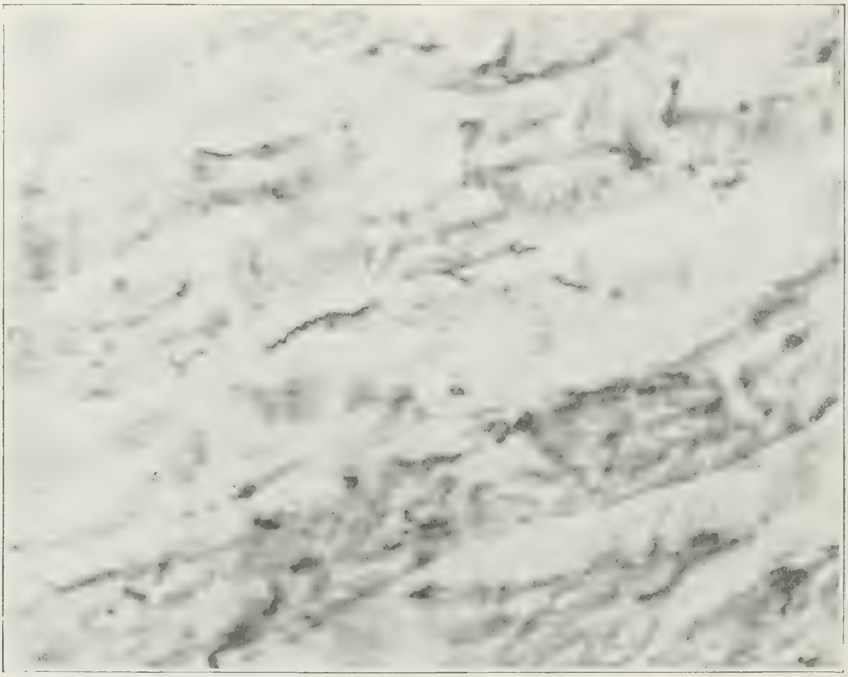

Fig. 12.—Levaditi preparation of active latent, unsuspected syphilis of left ventricle wall. Many spirochetes between muscle fibers.

Aorta.—The aorta, when examined microscopically, showed in every case of old syphilis characteristic syphilitic infiltrations in its media and adventitia. To the naked eye the changes may be very slight or marked. The gross appearances may be those of so-called senile atherosclerosis or of the type now generally recognized as syphilitic aortitis, or the two gross pictures were frequently combined in the same case, particularly in older patients. While the lesions in the majority of cases are most often seen in the beginning of the aorta and in its arch, they are often most marked in the abdominal aorta; and, in a few cases, were confined to this portion, so far as the gross appearances were concerned. The process is very common about the mouths of the aortic branches.

It is certain, from my experience, that the *gross appearances are no absolute criterion of the aortic condition. When the gross appearances of syphilitic aortitis are present the pathologic diagnosis of syphilis may be given at the autopsy table without hesitation; but when the picture is that of atherosclerosis, no positive exclusion of syphilis can be made without a microscopic examination.* The aorta may present no changes, or very slight ones, to the naked eye, but the microscopic investigation may show characteristic plasma cells along the vasa vasorum of the media and adventitia. This is true of all the early stages of the diseases. In the few cases of secondary syphilis examined at autopsy the aorta showed slight changes ("fatty degeneration of the intima"), or none at all, yet microscopic study showed extensive infiltrations along the vasa vasorum and around the small vessels in the prevertebral tissues. This is the early active stage when the demonstration of spirochetes can be most easily carried out. *The cases recognizable by the naked eye as syphilitic aortitis are old cases;* and the demonstration of the spirochetes in these becomes increasingly difficult. This is particularly true when to the syphilitic aortitis there are added the changes of atherosclerosis due to age or other etiologic factors. *In the great majority of old cases the gross appearances of atherosclerosis are combined with, and conceal those of syphilitic aortitis.* For this reason a negative diagnosis of syphilis of the aorta is of no value, in the absence of a thorough microscopic study.

The microscopic features of this form of aortitis are now so well known that they will be but briefly discussed here. Small infiltrations of lymphocytes and plasma cells are found along the vasa vasorum of the media and adventitia, usually most marked around the vessels of the latter, and diminishing in degree as the vessel passes up into the media. Perivascular proliferation, fibrosis and obliteration of the small vessel then follows. (See Figs. 16 and 17.) The resulting disturbances of nutrition of the vessel wall are first seen in the intima and the inner portion of the media, in the form of fatty degeneration, atrophy and necrosis of the cells of this portion of the vessel, with weakening and thinning of the wall, followed later by fibrosis and hyaline change. The involvement of the media progresses steadily outwards, and because of the greater involvement of the media locally there results local thinning of the vessel wall and microscopic ruptures of the elastic fibers. Such changes naturally predispose to the development of aneurysms. In simple uncomplicated syphilitic aortitis the fibrosis of the intima is less than in atherosclerosis, and there is less tendency to secondary atheroma and calcification. The two forms of aortic disease are, however, combined in the majority of cases, and the microscopic picture presents the characteristics of both processes. In some cases the changes in the intima and media really represent a slow anemic infarction due to the shutting off of the blood supply as the result of the obliterative endarteritis in the arteries of the vasa vasorum in the adventitia. The obliterated arterioles often appear as concentric formations resembling tubercles, miliary gummata or even suggesting epithelial formations. The lymphocytic and plasma-cell infiltrations are in the early stages most marked in the perivascular lymph spaces of the arterioles; but later these infiltrations often become very marked around the greatly dilated veins. A new formation of capillaries is often seen in the adventitia and outer portion of the media. These infiltrations often are large enough to be regarded as miliary gummata, but the development of well-defined gummatous nodules with caseating centers and giant cells is rare. When these do occur they are usually multiple.

The demonstration of spirochetes requires much time and patient search. I have found them in the aorta of acquired cases of syphilis only in the perivascular infiltrations of the adventitia. They occur usually in small colonies. In congenital syphilis, however, the intima of the aorta may show localized proliferations and infiltra-

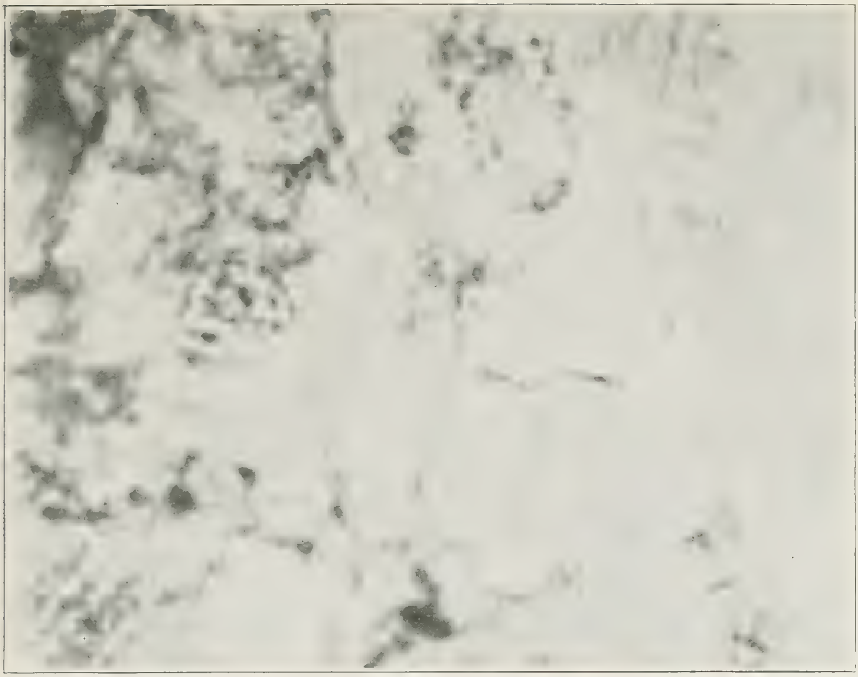

Fig. 13.—Levaditi preparation of chronic syphilitic myocarditis from case of unsuspected syphilis. Spirochetes at border of fibroid patch.

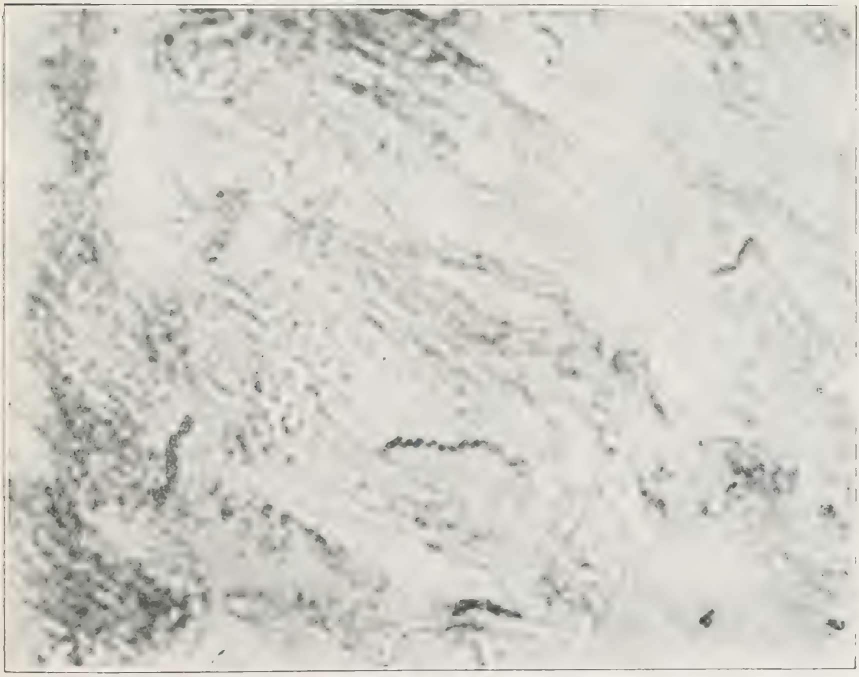

Fig. 14.—Levaditi preparation of chronic syphilitic myocarditis. Case of diabetes, syphilis not suspected, negative Wassermann. After prolonged search small colony of spirochetes found in small area of plasma cells at border of fibroid patch.

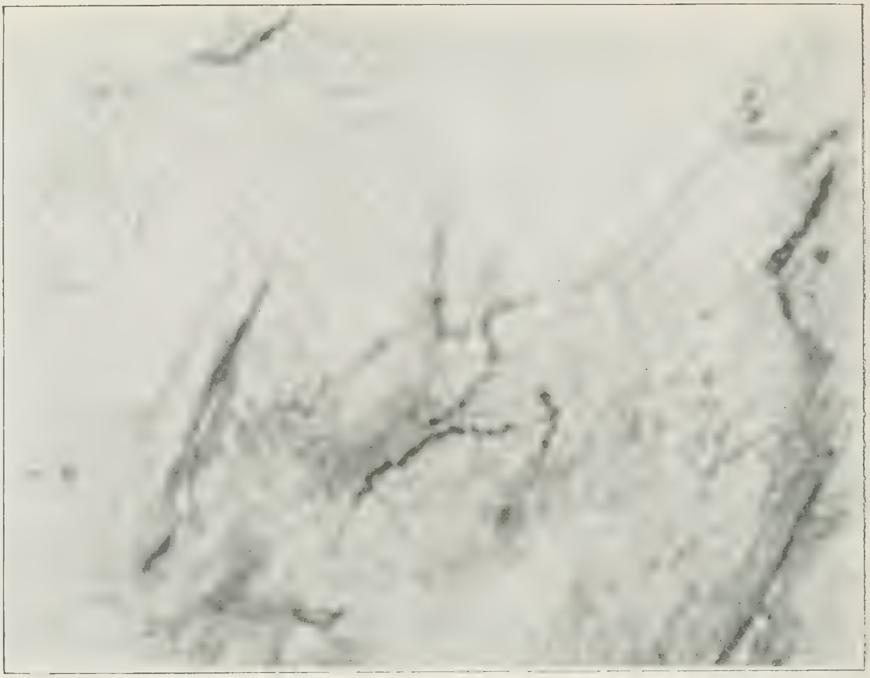

Fig. 15.—Levaditi preparation of fibroid heart from case of diabetes, with unsuspected syphilis, negative Wassermann. After six weeks search of blocks from left ventricle wall this colony of spirochetes was found at border of fibroid patch.

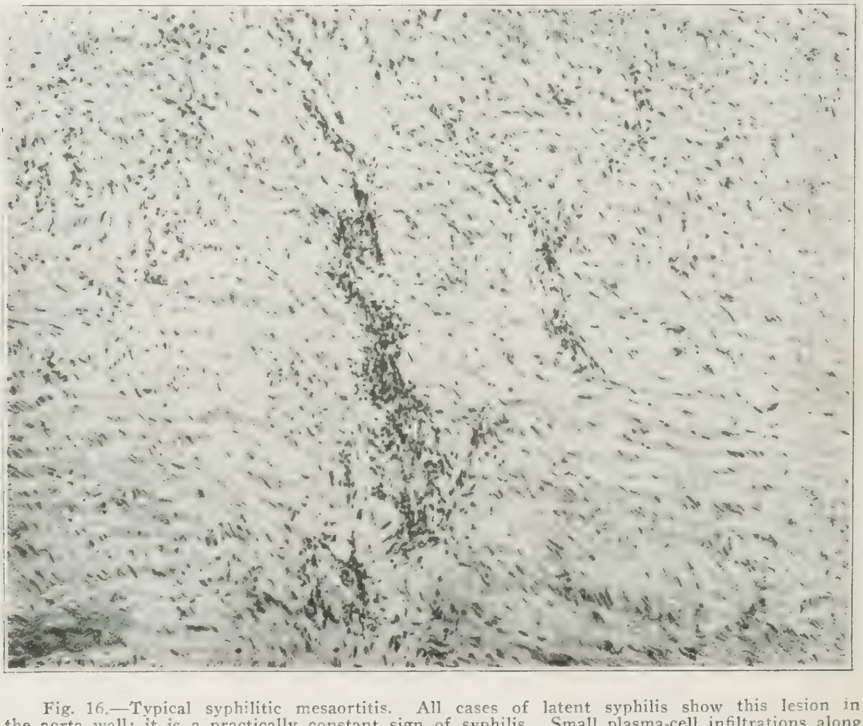

Fig. 16.—Typical syphilitic mesaortitis. All cases of latent syphilis show this lesion in the aorta wall; it is a practically constant sign of syphilis. Small plasma-cell infiltrations along the vasa vasorum, through the media of the aorta.

tions containing great numbers of spirochetes. In such congenital infections the syphilitic lesions of the intima may later heal and present the appearances of atherosclerosis. They then can not be distinguished from the local lesions of the intima found in typhoid fever and other infections.

Pulmonary Artery.—I have studied and reported a case of syphilitic aneurysm of the pulmonary artery with marked and characteristic syphilitic arteritis of this vessel and its branches. The presence of the spirochete was demonstrated in the aneurysmal sac, with blood clot in the wall. The organisms were found in very small numbers, possibly owing to the previous salvarsan treatment. The microscopic changes in the wall of the pulmonary artery were identical with those of syphilitic aortitis. How frequently such changes have occurred in the pulmonary artery in my cases I am unable to say, as no especial attention was paid to this vessel. In the microscopic notes on the lungs of these cases, there is frequent mention of thickened and hyaline pulmonary vessels; these changes were usually referred to the chronic passive congestion of the lung present in practically all cases. In but two other cases were there changes in the pulmonary artery so marked as to attract attention. One of these cases was that of a male who had had for some years a well-marked case of chronic cyanosis and polycythemia (Vaquez's disease). At autopsy his pulmonary arteries showed marked dilatation and atherosclerotic changes in the main branches with hyaline fibrosis and complete obstruction of many capillaries. The microscopic examination showed the presence of a typical syphilitic mesarteritis of the pulmonary arteries; and the polycythemia is explained as compensatory to the circulatory changes in the lung. This case undoubtedly falls into the group, of which a number have been reported from South America and India, of syphilis of the pulmonary arteries associated with polycythemia and cyanosis ("Ayerza's disease"). The other case of unusual atherosclerosis of the pulmonary artery showed microscopic changes of syphilitic arteritis without other complications.

Syphilis of Peripheral Arteries.—In several cases syphilitic arteritis of the femoral artery and its large branches, the popliteal and the tibial arteries was noted. In one case, a colored woman, the entire systemic arterial trunks and their smaller branches showed severe syphilitic arteritis with multiple thromboses. The abdominal aorta from the level of the diaphragm down and all of its branches contained organizing thrombi; globular thrombi were present in all four chambers of the heart. This case presented a condition not described in the literature—a very active generalized syphilis of the entire arterial system and heart. In all of these cases of syphilis of the larger arteries, the microscopic picture is identical with that seen in syphilis of the aorta and pulmonary arteries. There is the same lymphocytic and plasma-cell infiltration along the vasa vasorum of the media and adventitia with localized degeneration and fibrosis of the intima and inner portion of the media. In the smaller branches the entire vessel wall is involved and the process takes on the character of a proliferative endarteritis, as in the case of the arterial vasorum. The clinical importance of these arterial changes in this autopsy material has been chiefly that of aneurysm, thrombosis, embolism, infarction and gangrene, in about 5 per cent of the total number of autopsies; in the remaining cases no definite clinical symptoms could be ascribed to the aortic changes beyond the general circulatory disturbances common to all of the syphilitic cases, and which have been interpreted as chiefly cardiac in origin.

Pancreas.—The pancreas in all of the old cases of syphilis showed a greater or less degree of atrophy and interstitial fibrosis. In the majority of cases the changes were irregularly scattered throughout the organ, the body and the tail portions showing an especial tendency to involvement. Lobules showing marked change may be surrounded by those showing no change. In other cases the entire pancreas showed a diffuse fibrosis, varying from slight to the most marked degree. The connective tissue increase is both inter- and intra-lobular. In the majority of cases it was old, containing few cells; but in two cases of diabetes it was more fibroblastic in character and contained many cells of lymphocyte and plasma-cell type. Careful search has revealed, however, in every case active areas of plasma-cell infiltration. These areas often show an edematous or myxomatous connective tissue, the plasma-cells and lymphocytes may be few or many. Such inflammatory areas are most often found at the border of a lobule, and the latter are invaded by new connective tissue from the periphery usually, although occasionally the

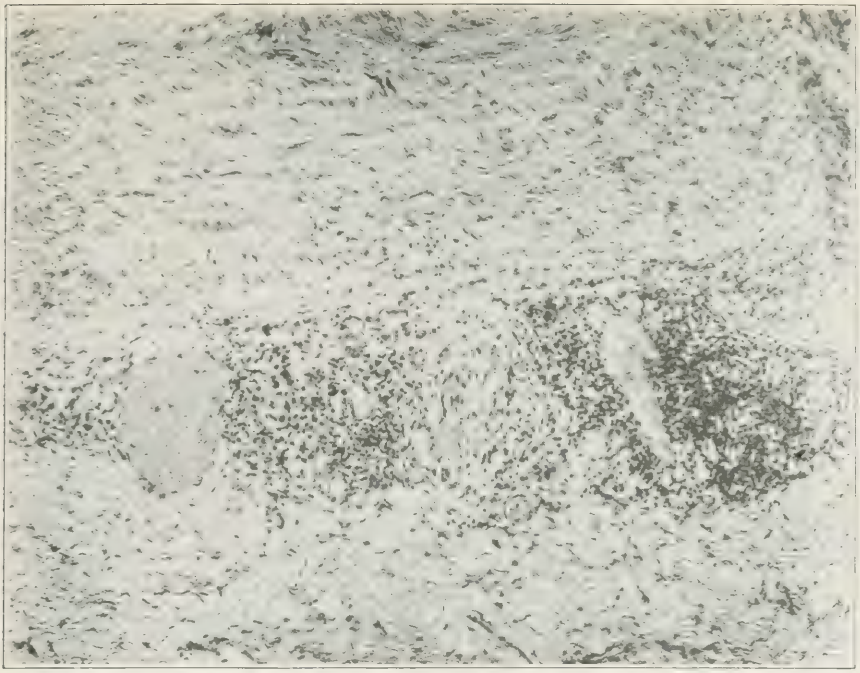

Fig. 17.—Portion of media and adventitia of aorta from case of latent, unsuspected syphilis. Characteristic plasma-cell infiltrations around the vasa vasorum, with obliteration of the small artery. One of the most constant and characteristic lesions of latent syphilis. Spirochetes are usually in small numbers and found only in these active foci.

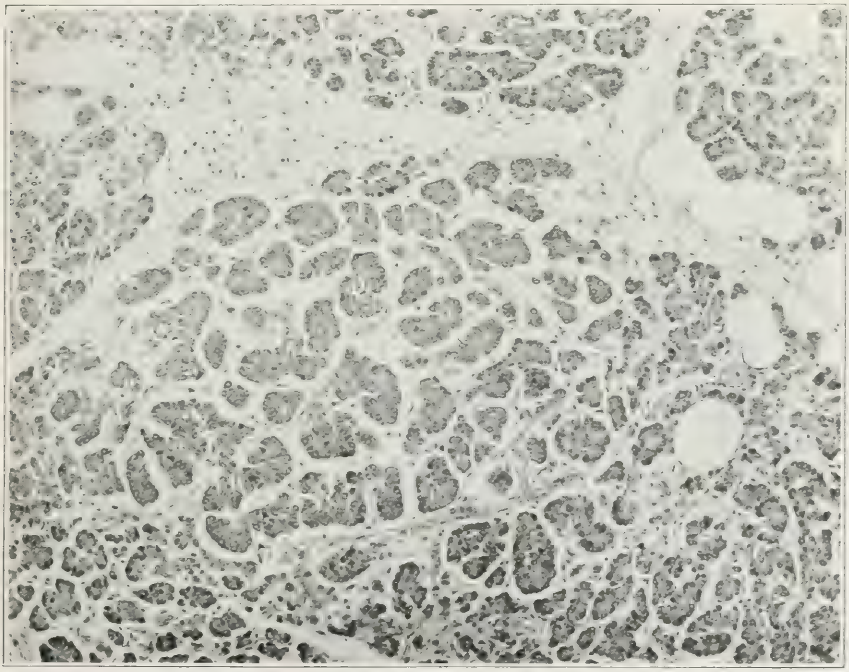

Fig. 18.—Pancreas from case of diabetes, with unsuspected syphilis and negative Wassermann. Diffuse chronic interstitial pancreatitis. Very small active areas, in which small groups of spirochetes were found.

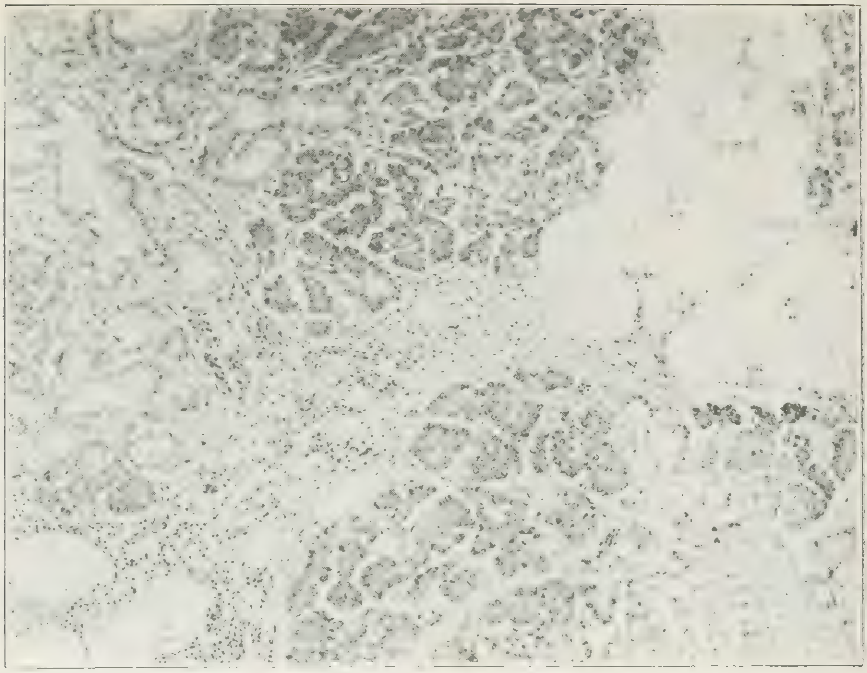

Fig. 19.—Chronic syphilitic pancreatitis, with active areas, from case of diabetes, unsuspected syphilis and negatve Wassermann reaction. Spirochetes found in heart and pancreas.

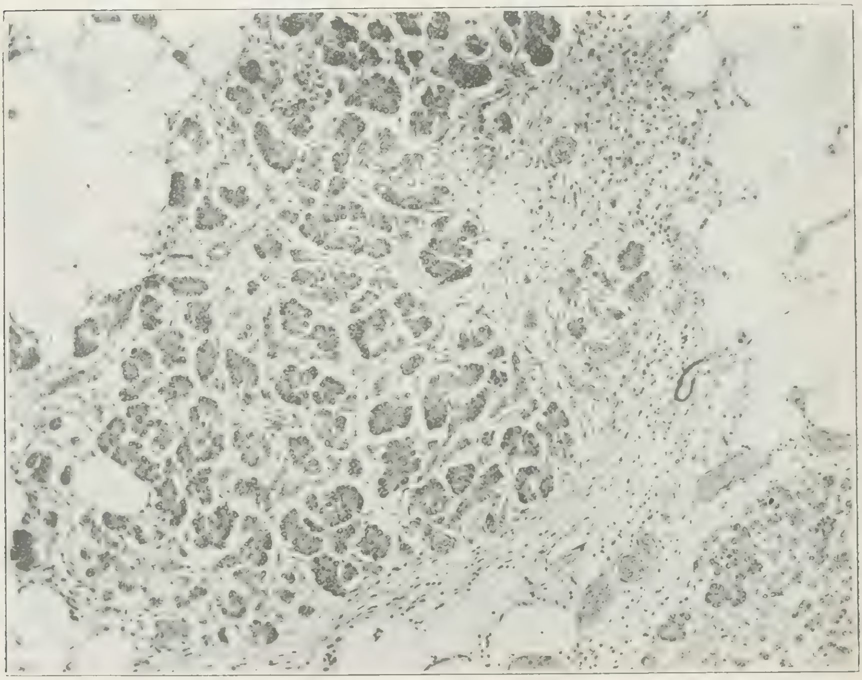

Fig. 20.—Chronic syphilitic pancreatitis. From tail of pancreas; same case as preceding.

process appears to begin within the lobule. Fibrosis of the islands in varying degrees is often associated with the interstitial inflammation. In all of the cases of diabetes but two, island fibrosis was very marked, and presented characteristic features, the chief of these being the thick crowding of large hyperchromatic cells around the border of the hyaline fibroid islands. These cells were interpreted as regenerative or hypertrophic. In several nondiabetic cases the chronic pancreatitis and fibrosis of the islands was as marked, or even more so, than in the diabetic cases.

The pancreatic acini show varying degrees of atrophy in the affected areas. As the acini disappear fat is deposited in the connective-tissue cells; in many cases such fatty infiltration following the atrophy of the pancreatic parenchyma is very marked. Islands completely surrounded by fat tissue are often seen in the tail portion of the organ. Regenerative formations may be found in practically every case; they often reach such a degree as to appear neoplastic, resembling adenomata or cystadenomata. The newly formed acini resemble islands and are undoubtedly often mistaken for newly formed ones. They arise from the epithelium of the lobular ducts and also from that of the larger ducts. Newly formed acini may even be found within dilated larger ducts. In every one of the cases of syphilis the pancreas showed evidences of progressive destruction and repair. No evidence of the new formation of islands, however, was ever seen. Sclerosis of the blood vessels of the organ may or may not be associated with the pancreatitis. Some degree of it was often found in the lobules showing marked interstitial change; but only in a relatively small number of cases was the inflammatory process associated with a general sclerosis of the pancreatic arteries. (See Figs. 18 to 26.)

As to the syphilitic nature of these lesions, they are identical with those produced by the spirochete in other tissues and organs. The localized plasma-cell infiltrations, slight fibroblastic proliferation, edematous or mucoid stroma, eventually fibrosis, are histologically specific characteristics, I believe; and in further proof of this view, spirochetes were demonstrated in these areas in the pancreas of two cases of diabetes.

So far as the clinical significance of these pancreatic changes is concerned the only fact of importance shown is their association with diabetes. In eleven out of twelve cases of diabetes coming to autopsy, the heart, aorta, pancreas, adrenals, (testes, in the males) and other tissues showed the characteristic plasma-cell infiltrations and fibrosis of latent syphilis. In five cases Spirochete pallida was demonstrated in the myocardium, and in two cases (Fig. 27) in the pancreas itself. In the pancreas they occurred in small colonies in the areas of cell infiltrations. That diabetes is the result of syphilis I do not venture to assert. If it is true that a chronic interstitial pancreatitis is the most common pathologic finding in the pancreas in diabetes, it seems very likely that syphilis is the most common cause of interstitial pancreatitis, but not necessarily, of course, the only cause. Syphilitic pancreatitis may be a common cause of diabetes, if it can be shown that interstitial pancreatitis is the essential pathology of diabetes.

Adrenals.—Small infiltrations of plasma cells and lymphocytes are of constant occurrence in the adrenals of cases having known syphilis and unsuspected latent syphilis. In the great majority of cases these infiltrations are slight. They occur usually in the medullary portion or in the inner portion of the reticular zone of the cortex. (See Fig. 28.) They are usually perivascular. Fibroblastic proliferation of the stroma or fibrosis may or may not be present; the capsule of the organ is usually thickened, and perivascular infiltrations of small size occur in the surrounding tissues. The walls of the blood vessels usually are thickened. Very rarely the infiltrations are so marked as to assume the characters of miliary gummata. Caseating gummata with giant cells have not been seen. In three cases the syphilitic infiltrations and fibrosis were so marked as to have caused nearly complete atrophy of the greater part of the organ. All three of these cases presented the symptom complex of Addison's disease. In one of these cases marked syphilitic infiltrations occurred also in the adrenal and semilunar ganglia. With the exception of these three cases no symptoms were observed that could be directly ascribed to the syphilitic changes in the adrenals. Whether in the less severe cases disturbances of adrenal function may be responsible for the low blood pressure seen in some of the cases it is, of course, impossible to say. Another striking feature of the adrenals in chronic syphilis is the marked lipoidosis of the cortex seen in so many cases. This lipoidosis may be patchy, involving certain cir-

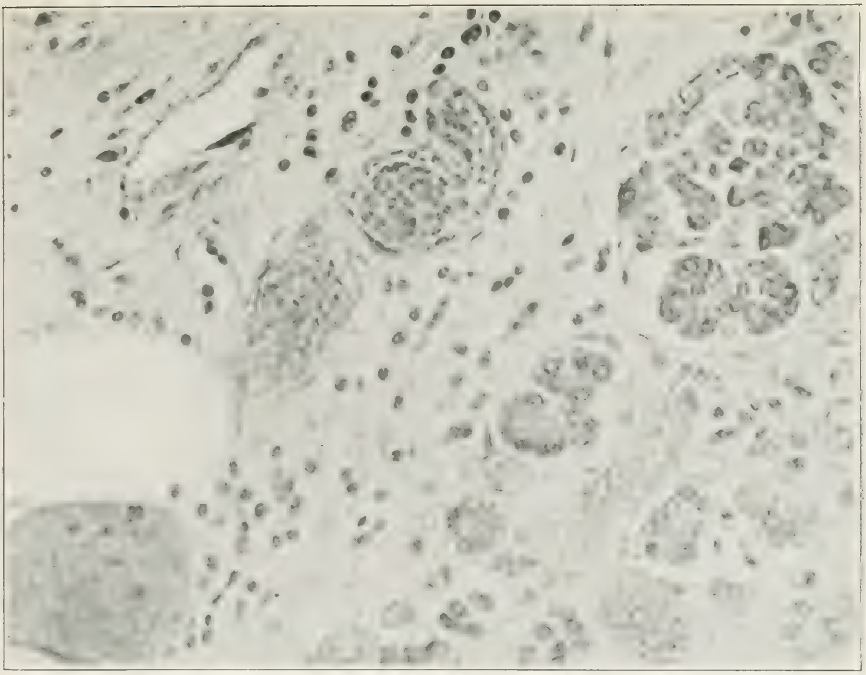

Fig. 21.—Chronic syphilitic pancreatitis. Higher power. Same case as preceding. plasma-cell infiltration; increase of stroma, and atrophy of acini.

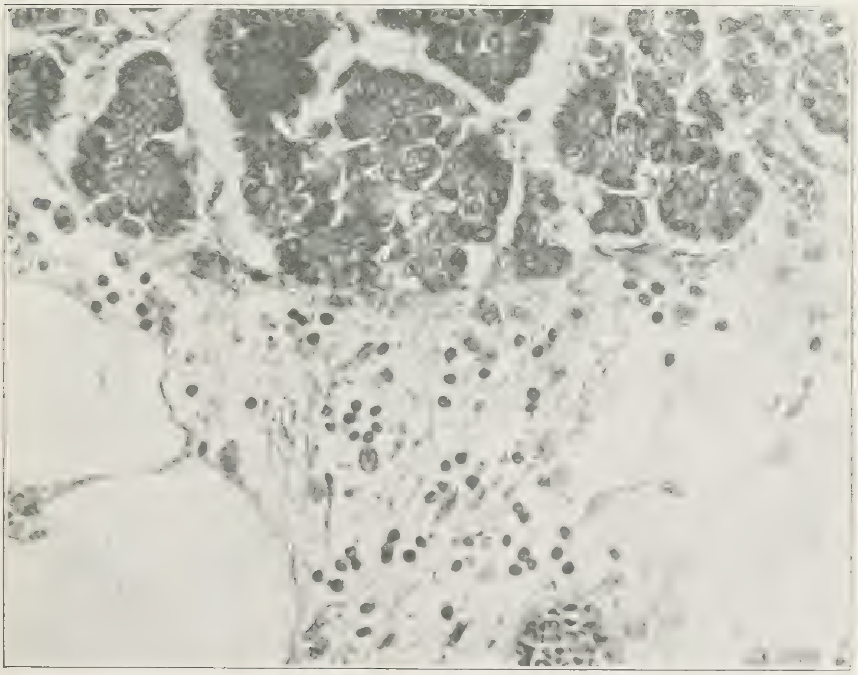

Fig. 22.—Chronic syphilitic pancreatitis. Same case as in Fig. 18. Small area of active plasma-cell infiltration and edema, in which spirochetes were found.

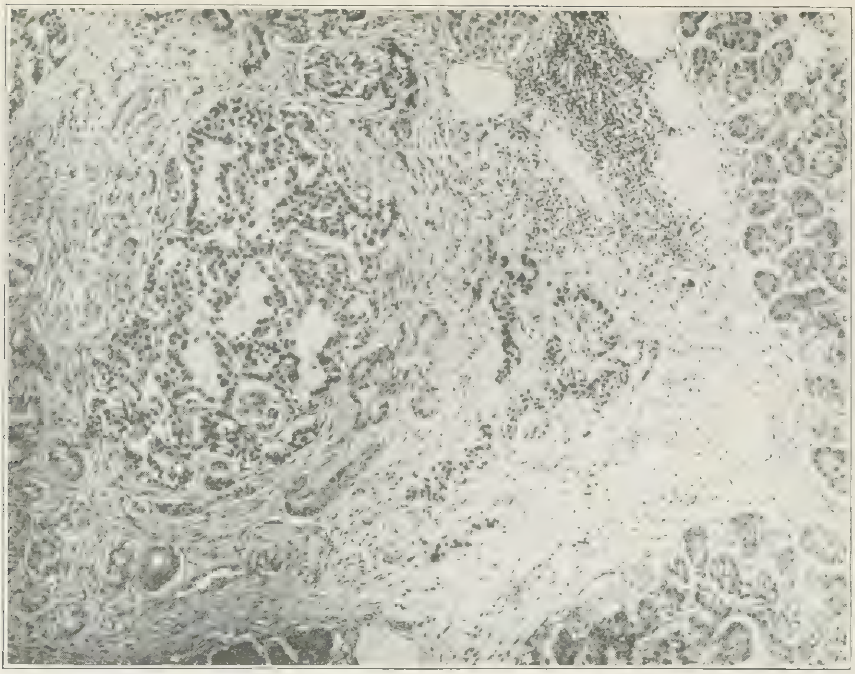

Fig. 23.—Chronic syphilitic pancreatitis. Same case, as in Figs. 19-21. Area of active syphilitic inflammation; new formation of pancreatic acini.

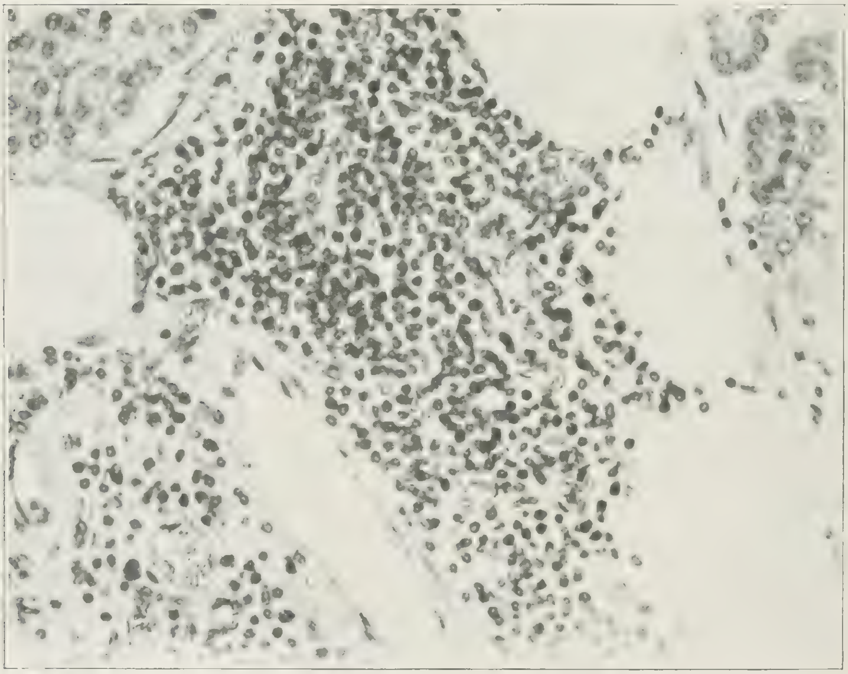

Fig. 24.—Chronic syphilitic pancreatitis. High power view of active area of plasma-cell infiltration seen in preceding.

cumscribed areas in the cortex, or it may involve the entire cortex. The cells are filled with numerous, large doubly refracting droplets that stain a brownish red with Sudan III and Scharlach R; with osmic acid many of the droplets take no stain, while others are grayish brown. The significance of this lipoidosis is not apparent, nor is its relation to syphilis. It is probably to be interpreted as an expression of a cholesterolemia or cholesterol retention, as a feature of a general disturbance of metabolism.

Liver.—The liver showed chronic passive congestion and atrophy (brown atrophy chiefly) in every case. Gummata were found in five cases, hepar lobatum in eight, atrophic cirrhosis in ten and an intralobular cirrhosis in one, Glissonian cirrhosis in three cases, while localized fibrosis was very common. The inflammatory lesions varied from slight plasma-cell infiltrations of the periportal tissue to the most marked cirrhotic changes. The relationship of these latter changes to syphilis has not been absolutely determined except in a few cases in which spirochetes were found in such infiltrations. It is worthy of note that in a case of secondary syphilis dying of salvarsan poisoning focal necroses containing spirochetes were present throughout the liver. (See Fig. 29.)

Testis.—In all of the male cases the testes showed varying degrees of atrophy and fibrosis. In the more active cases plasma-cell and lymphocyte infiltration between the tubules, fibroblastic proliferation of the stroma, thickening of the basement membrane and diminished spermatogenesis are the chief changes. (See Fig. 30.) These changes may involve the entire organ, or occur in small scattered patches. In the older cases the germinal epithelium of the tubules may be entirely lost, the tubules collapsed, and represented entirely by the hyaline thickened basement membrane which still keeps the shape of the tubule. The interstitial cells remain preserved, and in many cases appear hypertrophic. The stroma between the tubules is thickened and hyaline. (See Figs. 31 and 32.) In severe cases the entire testis becomes fibroid. Spirochetes can be demonstrated only in the active cellular infiltrations. So far as size, shape, and consistency are concerned, the gross appearances of the affected organs may seem to be normal. The clinical significance of these changes is a progressive loss of spermatogenesis and virility. Many of the patients had complained of premature loss of sexual desire.

Other Lesions.—Throughout the *prevertebral tissues, root of mesentery,* along the *radicles of the portal vein,* and in the *pelvic tissues* there constantly occur in the bodies of old syphilitics minute perivascular infiltrations of lymphocytes and plasma cells, associated with fibroblastic and angioblastic proliferations, eventually fibrosis, of a more or less marked degree. That the spirochete is associated with these minute lesions has been definitely proved. Therefore, in all cases in which these occur the possibility of spirochete localization must be considered. Such minute syphilitic inflammations may be widespread; they may be found in any tissue or organ.

Lungs.—The occurrence of syphilitic localization in the lungs was positively determined in three cases only, in which there were vascularized granulomatous areas, gummatous in character. No especial study has been made of this organ. In nearly every case the lungs showed chronic passive congestion and more or less marked induration or fibrosis. This has usually been interpreted as the result of the chronic passive congestion. As other writers have already pointed out, this fibrosis of the lungs may be directly the result of syphilis; but to what extent this has been true in this autopsy material I have not had time to determine. The question should, however, be taken up by investigators, as our knowledge of syphilis of the lung is very fragmentary and vague.

Spleen.—Chronic passive congestion, atrophy, and sclerosis of the splenic arterioles are the almost constant findings in the spleens of old syphilitics. Gummata were found in three cases; and these were the only positively determined instances of spirochete localization in this organ. This is also a field requiring investigation. I have been unable to extend my studies to this organ.

Kidneys.—Changes in the kidneys—chronic passive congestion, atrophy, infarctions, local and diffuse inflammations—were found in practically all kidneys coming from these cases. The proportion of cases of chronic parenchymatous nephritis is very striking. Out of the first forty-one cases of this material studied there were seventeen cases of acute, subacute and chronic parenchymatous nephritis, and three cases of interstitial nephritis. The relation of these conditions to the syphilitic infection is not apparent. I have never found spirochetes in the kidney, but they have been looked for in only a few cases. This is also a field demanding investigation.

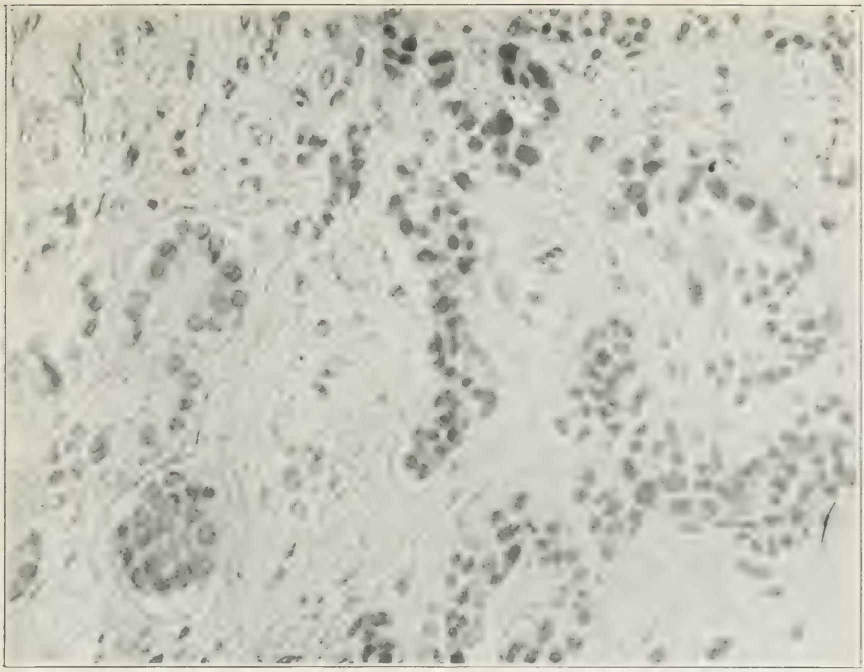

Fig. 25.—Chronic syphilitic pancreatitis. High power, showing fibroid stroma and atrophy of acini. Healed, inactive area.

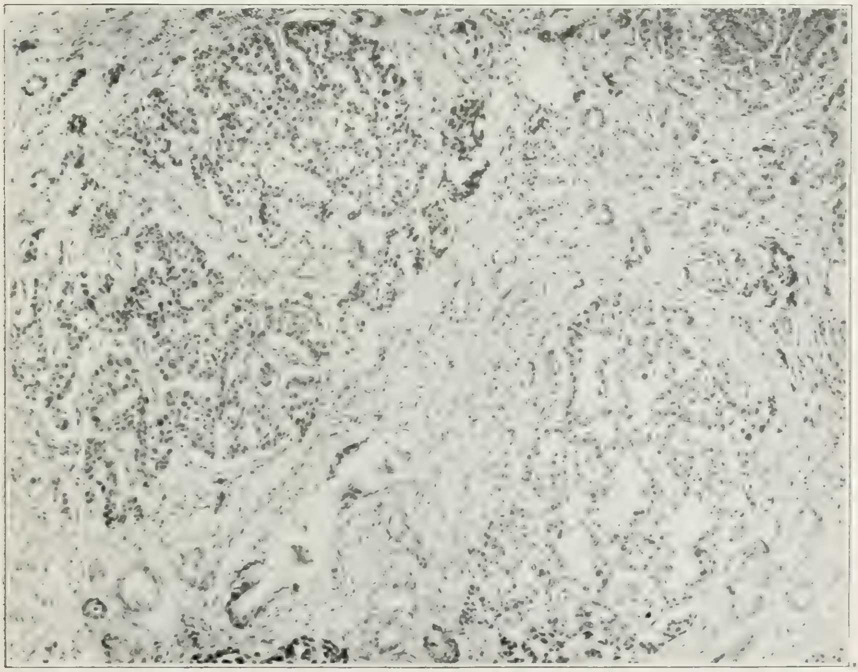

Fig. 26.—Chronic syphilitic pancreatitis. Area of severe change; fibrosis, destruction of pancreatic tissue and atypical regenerations of acini from pancreatic ducts. Such newly formed acini are usually mistaken for new islands of Langerhans.

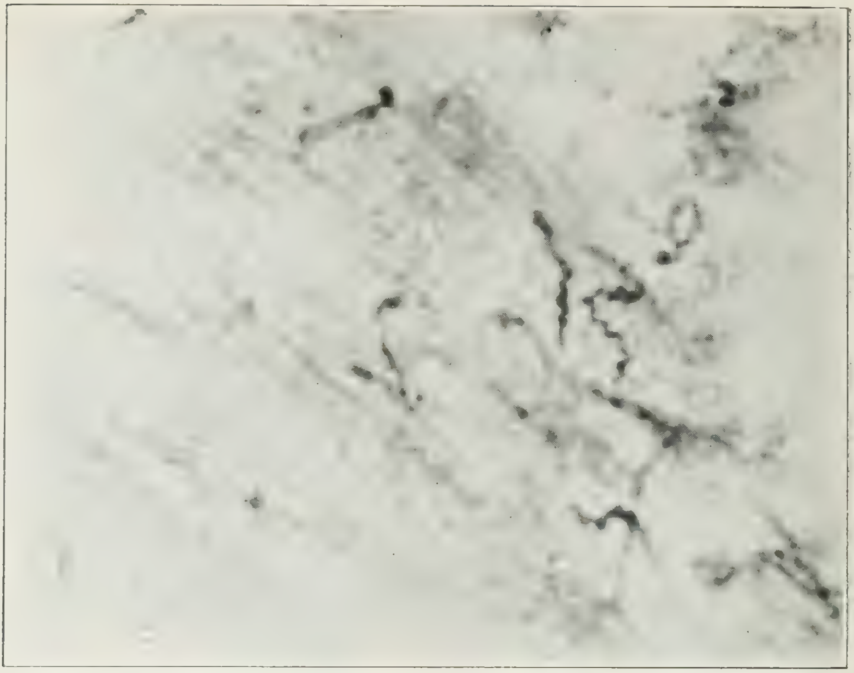

Fig. 27.—Colony of spirochetes in edematous, infiltrated area between lobules.

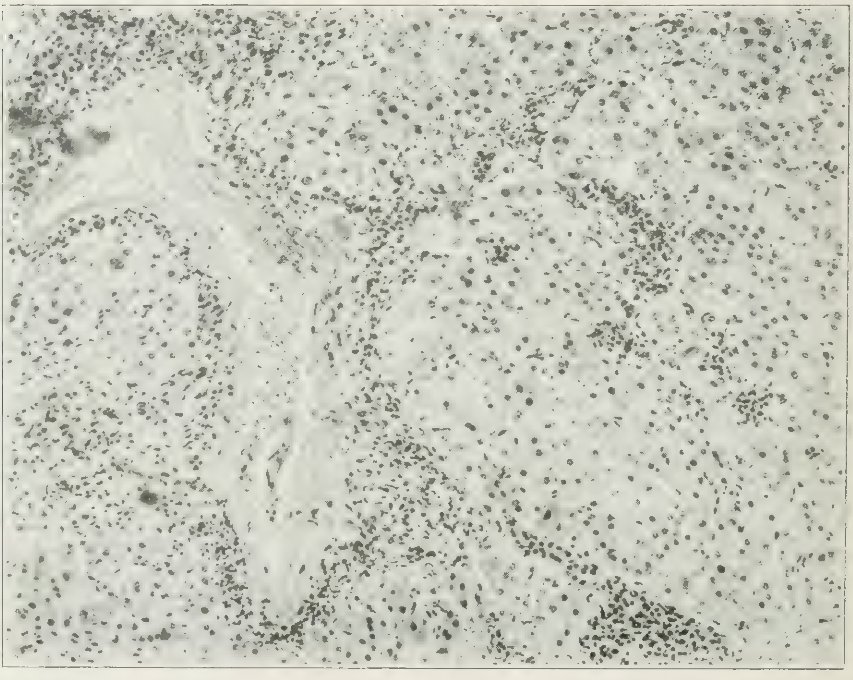

Fig. 28.—Syphilis of the adrenal. Plasma-cell infiltrations in inner zone of adrenal cortex and in medulla. One of the most constant findings in latent syphilis. These infiltrations are usually much less marked than in this case.

Genital Apparatus.—Outside of the testes spirochetes have been found in the sexual apparatus of the cases in this material once only, and that in the prostate of a young man with early tertiary syphilis clinically latent. Diffuse plasma-cell infiltrations occurred throughout the stroma of the organ, and not around the gland spaces as in chronic gonorrhea. The infiltrations were perivascular, interstitial, and not periglandular or subepithelial. Fibroblastic and angioblastic proliferations were prominent, and numerous giant cells occurred in the larger infiltrations, giving them the characters of miliary gummata without caseation. Groups of spirochetes were found in these. This case was the first one in which syphilitic lesions of the prostate were positively demonstrated. No spirochete study has been made of other portions of the internal reproductive tract in either sex.

Lymph Nodes.—The lymph nodes of the older cases of syphilis (even in young individuals) were atrophic and presented lymphoid atrophy, chronic sinus catarrh and hyaline formations (scars) in the germ centers and lymphoid tissue. In younger cases the nodes are frequently hyperplastic, but the germ centers, while enlarged, show a marked lymphocyte exhaustion. These appearances indicate a continuous demand made upon these organs against a persistent infection.

Bone Marrow.—Premature and excessive osteoporosis of the bones, and fatty atrophy of the marrow characterized the majority of cases. In a small number of cases the lymphoid marrow was found to be increased.

Hemal Nodes.—These were atrophic, in the great majority of cases. In association with marked anemia, and syphilis of the portal vein with Banti's disease complex, a marked hyperplasia of these nodes was seen, with great numbers of hemophages blocking the sinuses.

SUMMARY

The pathologic lesions, as described above are common to all cases of old syphilis (secondary stage onwards). They were found in known active cases of late syphilis (aortic aneurysm, gumma of brain and liver, tabes, paresis, etc.), in cases with history of syphilis treated and regarded as cured, in cases with negative and cases with positive Wassermann reaction; and, in the great majority of autopsies, in the bodies of those who gave no history of syphilis and no clinical signs or symptoms interpreted by the clinicians as indicating syphilis. It is probable that many of these patients never knew that they had syphilis; the infection in some cases is probably congenital, in others accidental. In other patients the previous infection may have been entirely forgotten or supposed to have been entirely cured. As syphilis is a "skin disease" to the average mind, both lay and medical, the symptoms predominating in this class of patients were not likely to arouse any suspicion of any relationship to the old infection, unless excited to such suspicions by direct and intensive questionings along this line, which they failed to receive.

It is, therefore, evident that syphilis as a latent infection is very much commoner than is generally supposed; and that the proportion of syphilitics in our ailing class is very high. It is, perhaps, idle to estimate the number of cases of syphilis in our population. To my mind the estimates of 5 to 15 per cent given by various writers are all too low; we would place the incidence of syphilitic infection in this country as nearer 30 per cent. An analysis of our vital statistics will easily show that at a very low estimate about one-tenth of all the deaths occurring in the United States can be attributed to syphilis. Dr. Osler has recently made a similar estimate for Great Britain. Syphilis is the leading infection and the chief cause of death, even when estimates are based upon our incomplete and imperfect knowledge of the pathology and symptomatology of the disease after the chancre and skin-symptom stages have been passed through. Death is rare in the first two years after infection with syphilis; the incidence of syphilitic death increases progressively with the years after the infection. Syphilis is particularly the cause of death in males between forty and sixty years of age; and as its symptomatology at this stage is in the great majority of cases either myocardial, vascular, renal, hepatic, etc., it is not recognized clinically as syphilis.

It is, further, very evident that infection with syphilis means *spirochete-carrying* in many, if not in all cases. The cases in the material analyzed in this study represent "*spirochete carriers*," and the pathology given above is the pathology of a mild latent infection in which there is but little antagonism between the infecting organism and its host. Syphilis after a preliminary invasion and disturbance of the body tends in the great majority of cases prob-

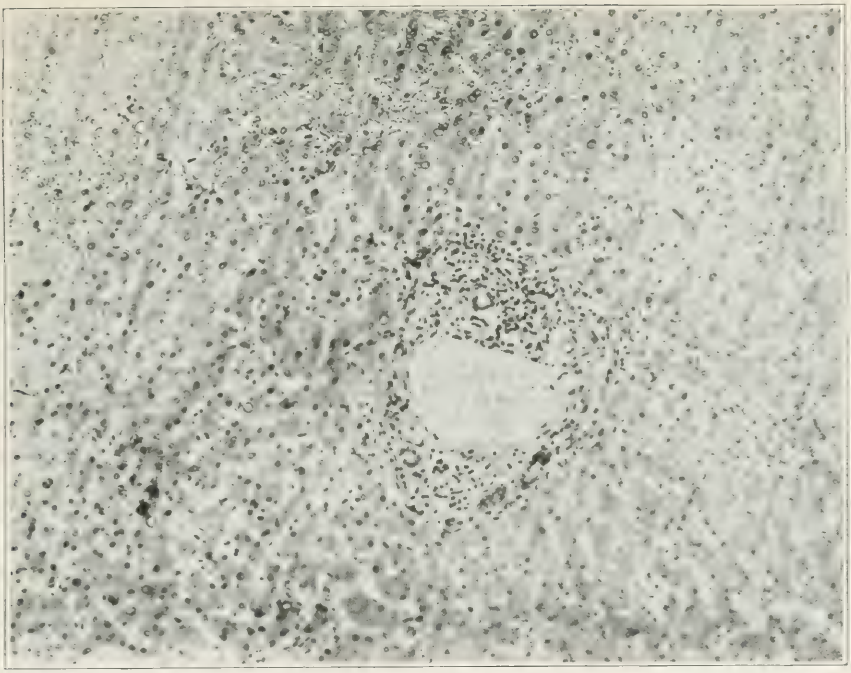

Fig. 29.—Liver from case of latent syphilis. The most constant and the mildest syphilitic lesion of this organ. Slight plasma-cell infiltration of periportal tissues. Every degree from this very slight lesion, up to the most severe grades of cirrhosis presents itself in syphilis.

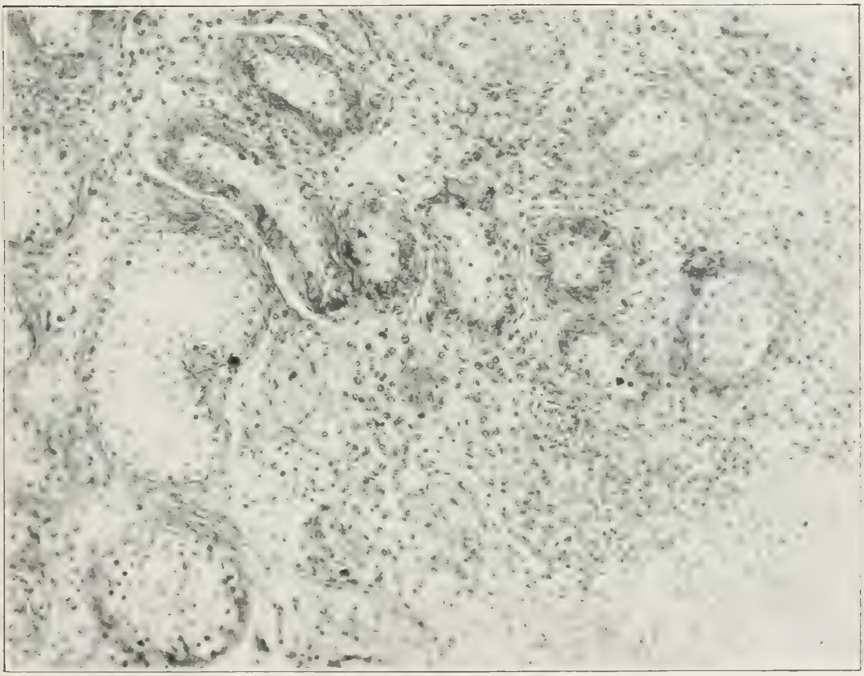

Fig. 30.—Active syphilitic orchitis. A constant lesion in all old cases of latent syphilis. Varies greatly in degree and extent. Spirochetes found only in active areas, as in this case.

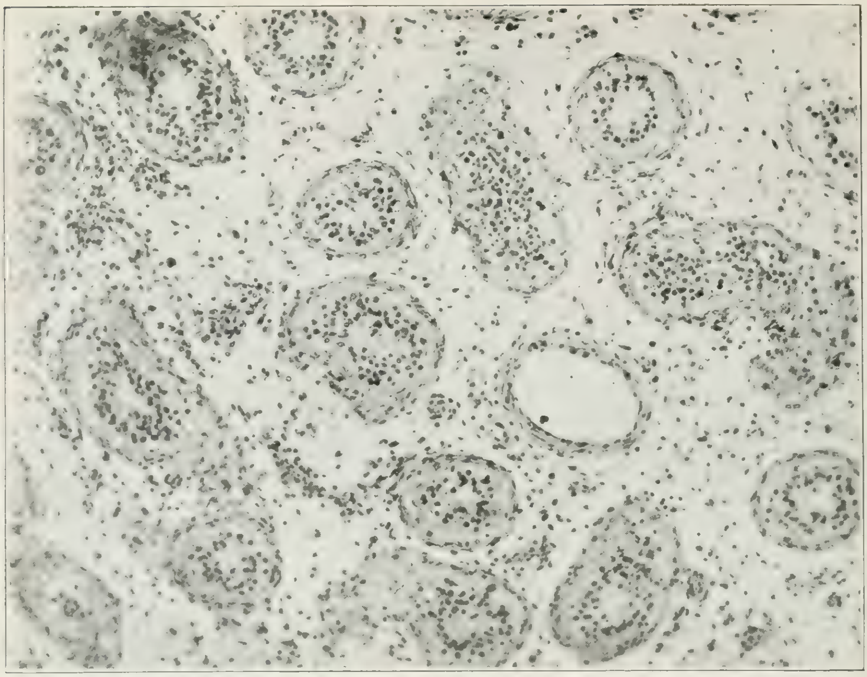

Fig. 31.—Subacute syphilitic orchitis. Increase of stroma; atrophy of germ cells; hyaline thickening of basement membrane of tubules; active syphilitic infiltrations. From case of congenital syphilis. Patient, aged 19 years.

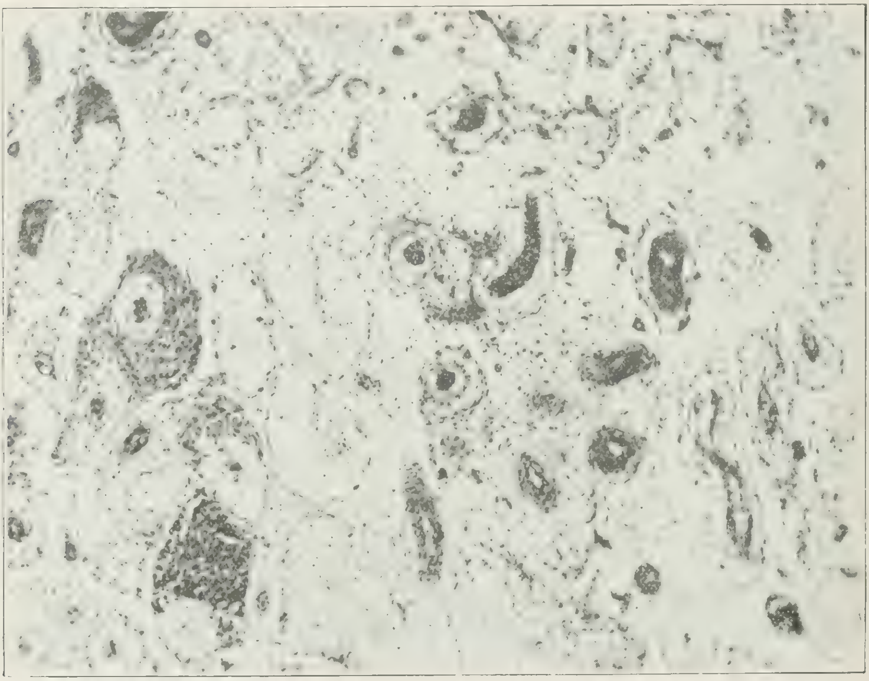

Fig. 32.—Chronic syphilitic orchitis. Complete fibrosis of testis, hypertrophy of interstitial cells. From same case as Fig. 6.

ably to become an infection not much more active or injurious than the streptococci of the mouth cavity. The very slight lesions found in so many cases prove this point beyond dispute. In women, particularly, does the infection often become so mild as to be practically nonexistent, except when pregnancy occurs and there is born a syphilitic child, or a syphilitic abortion or stillbirth occurs, with spirochetes in placenta, fetus, or child. *The spirochete carrier is immune to new infection only as long as he carries spirochetes.* This axiom we accept today, but we are yet far from understanding the reactions between the host body and the parasite spirochete. The individual tissue immunities and susceptibilities that undoubtedly exist, the reawakening of virulence on the part of the quiescent organism, its relationship to the Wassermann reaction, the question of positive cure, etc., are chief among the unsolved problems connected with this most important of all infections.

As to curability, I have never seen pathologically a cured case of syphilis. In all cases examined at autopsy active areas of specific inflammation are always seen, and such areas mean always the persistence of the spirochete. Perhaps these intratissue parasites should in cases without symptoms and negative Wassermann reaction be regarded in the same light as that in which we look upon the streptococci of the mouth cavity. Does the spirochete cease to be a cause of disease, and the body become a carrier of relatively or even quite completely harmless organisms? That some progressive injury is being caused is demonstrated conclusively by these studies. Immunity to the Spirochete pallida, and probably to all other organisms that enter the body tissues or, perhaps, even its passages and cavities, is paid for with a price—the price of defense. The infiltrations of lymphocytes and plasma cells in themselves may cause damage—infinitesimal, perhaps—but when persistent over a period of years may finally produce functional disturbances. The persistent slight damage and necessary repair by fibroblastic proliferation and the eventual fibrosis explains the latent period of syphilis and the final outcome in such terminal conditions as aortitis, myocarditis, pancreatitis, etc. The majority of cases of syphilitic infection die from the results of these slow mild inflammatory processes in the viscera and blood vessels rather than from paresis or tabes. I am convinced that the great majority of all cases infected with syphilis die of *chronic myocarditis.*

The syphilitic is pathologically "damaged goods;" and the damage is a progressive one. He wears out sooner, his viscera more quickly reach their histogenetic limits, he actually becomes prematurely old, and there is a constant strain upon his defensive powers. All of these are arguments for the prevention of syphilitic infection rather than for its cure. No man can acquire syphilis, become clinically cured, which as far as we know means latency of the infection, that is, spirochete carrying, and have the same potential body-value and expectancy of life as before the infection.

This pathologic conception of the syphilitic, as probably always a spirochete carrier once the infection is acquired, should influence the therapeutic management of this chronic infection. The syphilitic, even when apparently perfectly well, should have his life laid out for him along lines tending to prevent the reawakening of the virulence of the organism or an increased susceptibility of the body tissues and organs. This is done for the patient who has once had clinical tuberculosis; when properly treated his future life is planned to prevent the reawakening of his infection, because he, too, is usually, if not always, still a carrier of the infective agent. But in the case of the syphilitic such hygienic measures are not applied, implicit reliance is usually placed upon a certain amount of salvarsan or mercurial treatment, while the infected invidual is permitted to take up his life again as if he were an ordinary individual, and, as a rule, he succumbs prematurely to the stress and strains incident even to ordinary living. The treatment of syphilis, as it is ordinarily carried out, looks only to the present moment; it should look to the whole future life of the infected individual.

Syphilis in the woman presents peculiar problems. In the great majority of women infected with this disease it runs an absolutely latent course; the lesions at autopsy in the heart and aorta are always, except in rare cases, much milder than in man. Such women die of secondary infections or other conditions, rather than of myocarditis or aortitis. The pancreas and adrenals are, however, affected to the same degree as in man, the adrenals perhaps more so. A syphilitic woman may, however, pass her entire life without any clinical manifestations of syphilis, except the produc-

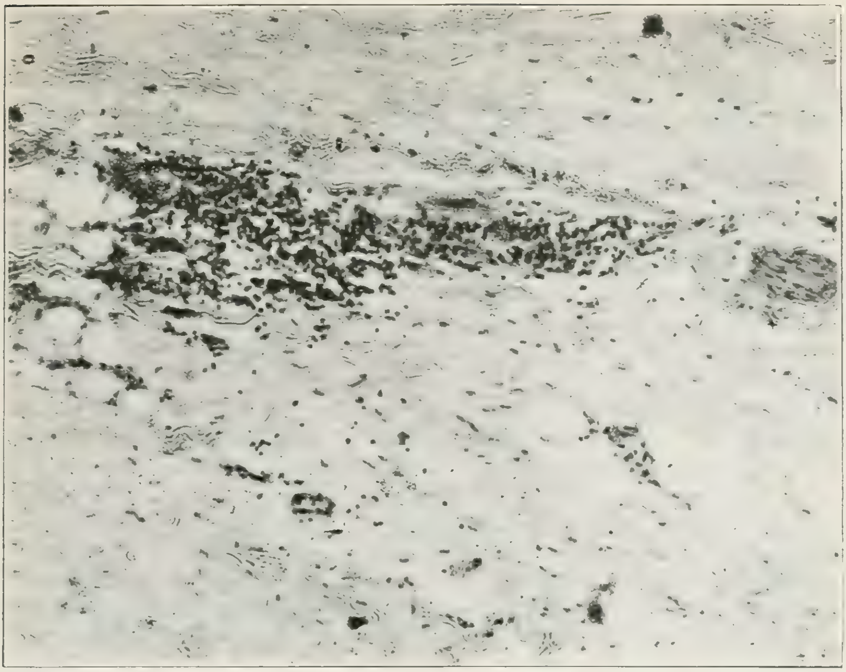

Fig. 33.—Syphilitic infiltrations in prevertebral tissues. Common findings in all old latent cases.

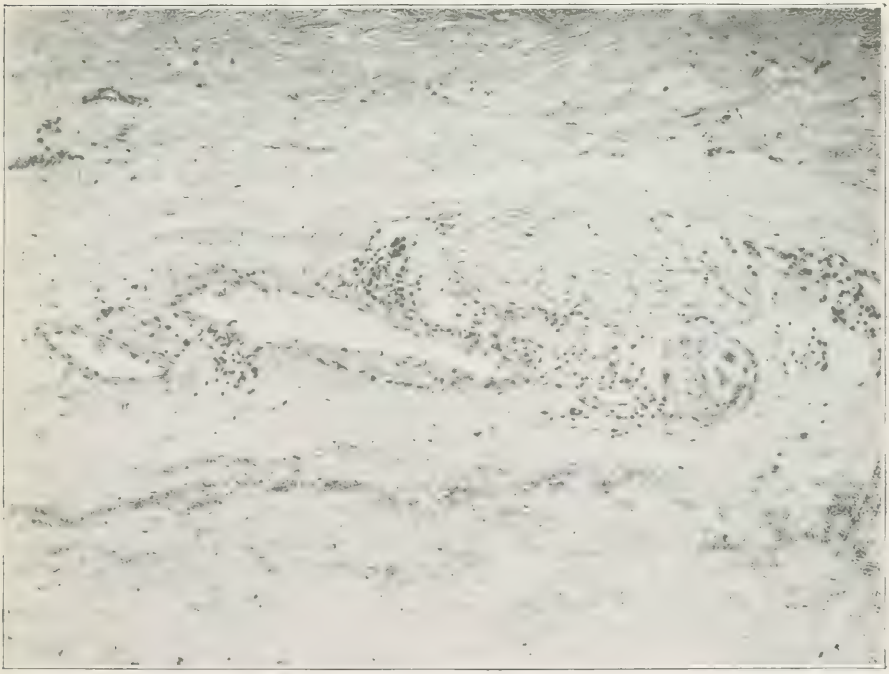

Fig. 34.—Small syphilitic infiltrations of plasma-cells around nerve trunk and vessels in root of mesentery. These are common in all old cases of active latent syphilis and are found particularly near the abdominal aorta and solar plexus.

tion of syphilitic progeny. I have come into touch with numerous examples of this kind, of which a few may be cited here.

1. Wife of a school teacher gave birth to a dead child. Autopsy of the infant revealed syphilis of the liver, and spirochetes. Both father and mother were above suspicion, absolutely negative histories, no signs, repeated Wassermanns of both negative. Pathologic diagnosis of syphilis not accepted by clinicians. Woman without treatment was allowed to become pregnant again and in a little over a year was again delivered of a dead and macerated fetus showing syphilis of liver and heart, and spirochetes. Repeated Wassermanns of both father and mother were negative. The only explanation of this case that could be obtained was in the fact that the father of the mother had been a chronic drunkard since youth.

2. Case similar to above. Two syphilitic children from father and mother, both apparently healthy, no history and no signs of syphilis, negative Wassermann in both. Father of mother a chronic drunkard since early manhood.

3. Father and mother apparently healthy, no signs and no history of infection, negative Wassermann in both, repeated abortions, one living child dying a few months after birth of congenital syphilis of liver, spleen and heart. The history of this case brought out the fact that the mother's father had been a chronic drunkard, "a beast," and diseased. Mother as a very young child had been rescued from the family conditions and brought up by a relative. A sister left behind became a keeper of a house of ill fame.

4. Grandfather on both sides a chronic drunkard. Father and mother apparently well, no signs of syphilis, negative Wassermanns in both. Three apparently healthy children, although minute examination reveals certain stigmata in bone development, then a child dying of active syphilis, then two more children apparently well, then a dead dropsical fetus showing a marked syphilitic placenta.

5. Father a preacher, no history or signs of syphilis, negative Wassermann; mother's father had "blood poisoning," mother herself apparently well, negative Wassermanns repeatedly. Three syphilitic miscarriages.

It is very probable that in each of these cases the mother had congenital syphilis from her father. When there is a history of chronic alcoholism, syphilis is almost invariably present too. I believe that congenital syphilis in the woman is particularly likely to run a mild latent course without clinical manifestations, but that during the early months of pregnancy the spirochetes gaining entrance to the fetal circulation may regain their virulency and cause abortion, miscarriage, stillbirth or give rise to active clinical syphilis in children born alive. Such children may show the infection at birth or later.

It is very difficult to demonstrate spirochetes in the placentas of syphilitic children born at or near full term. In the fibroid villi they can not be found. In the young, myxomatous hyperplastic villi of the syphilitic abortion occurring in the early months of pregnancy they are demonstrated more easily. I have found syphilitic lesions and spirochetes in placenta and tissues of a dead macerated fetus coming from a mother thoroughly treated with salvarsan according to modern methods, said by an expert in syphilology to be cured, and told that she might have healthy children. The first child was a syphilitic. It is also of interest to note the apparent fact that the tissues of the macerated fetus appear to be a good culture medium for the spirochete.

The constant occurrence of syphilitic lesions in the testes of latent syphilitics throws light upon the clinical facts, already known, that such cases may transmit the disease, and show spirochetes in their semen. The pathologic findings warrant the assertion that any individual who has had syphilis is particularly likely to pass out spirochetes in the semen and cause a seminal infection of woman or child. The localization of the spirochetes in the basement membrane of the seminiferous tubules makes this form of transmission practically a certainty. It is very probable that the great majority of cases of congenital syphilis are seminal infections of the mother and placental infections of the fetus.

So far as the Wassermann reaction is concerned I believe that a well-marked positive reaction indicates syphilis, with very few exceptions, such as generalized carcinomatosis, sarcomatosis, etc. In these conditions a 4-plus reaction may be found without any autopsy signs of syphilis. A negative reaction can not be taken as indicating the absence of syphilitic infection, nor can repeated negative reactions. I have repeatedly found active lesions of syphilis with spirochetes present when the reaction was negative. This is particularly true of gumma of the brain and congenital syphilis. As has been frequently noted the blood reaction is frequently negative in brain and cord syphilis when that of the spinal fluid is positive. I have had an opportunity of examining the bodies of eight cases dying from salvarsan poisoning; three of these were children with congenital syphilis, and of the five adult cases, three had syphilis of the central nervous system and had intradural treatments. In the congenital cases the treatment apparently had not in the slightest degree affected the number of spirochetes. In two of these cases the tissues throughout the body were swarming with spirochetes. In an adult case with secondary lesions the liver contained multiple focal necroses with spirochetes present in the necrotic areas. It is a question as to whether these focal necroses were due to the spirochetes primarily or to the action of the arsenic. In all cases death was apparently due to the toxic action upon the renal epithelium.

CONCLUSIONS

1. The gumma is not the essential typical lesion of old or latent syphilis. It is a relatively rare formation; and the great majority of cases of syphilis run their course without the formation of gummatous granulomata.

2. The new pathology of syphilis is based upon the demonstration that the essential tissue-lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma-cell infiltrations in the stroma particularly about the blood vessels and lymphatics, slight tissue proliferations, eventually fibrosis, and atrophy or degeneration of the parenchyma.

3. These mild inflammatory reactions are due to the localizations in the tissues of relatively avirulent spirochetes.

4. Syphilitic inflammations of this type occur in all tissues and organs; but are most easily recognized in the nervous system, heart, aorta, pancreas, adrenals, and testes. They are, however, usually widely distributed throughout the entire body, although in individual cases showing especial predilection for certain organs or tissues. No explanation of these system, organ, or tissue predilections is yet evident; neither is there any explanation of those cases in which all organs and tissues show the most severe degree of these lesions.

5. The syphilitic is a spirochete carrier. In this respect, the Spirochete pallida is to be classed with the trypanosome, the malarial organisms, lepra and tubercle bacilli, streptococcus, etc.

6. Syphilis tends to become a mild process; but at any time the partnership between the body and the spirochete may become disturbed, and tissue susceptibility or virulence of the spirochete become increased so that the disease again appears above the clinical horizon.

7. Immunity in syphilis depends upon the carrying of the spiro-

chete. A price is paid for this immunity in the form of the defensive inflammatory lesions previously described.

8. The disastrous effects of syphilitic infection usually require a period of years for their development. The slowly progressive lesions, fibrosis and atrophy, may at last manifest themselves in paresis, tabes, myocarditis, aortitis, aneurysm, diabetes, hepatitis, or in many other forms of tissue damage and functional disturbance. Lesions of the viscera are much more common and important clinically than those of the central nervous system, but they are rarely recognized as syphilitic by the clinician. Syphilitic death occurs most frequently in males between the ages of forty and sixty. Chronic myocarditis is the most common form of death due to syphilis.

9. The pathologic diagnosis of syphilis is essentially microscopic. Only in a relatively small number of cases are the gross lesions (tabes, gumma, aortitis, etc.) typical enough to be recognized by the naked eye. A negative diagnosis of syphilis can not be given with any certainty without a routine microscopic examination of all organs and tissues, but particularly of the left ventricle wall, the aorta, both its arch and abdominal portion, the testes, pancreas, and adrenals.

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